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L3 ANSWER 1 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
1998:282401 Document No. 128:321653 Preparation of alkynyl- and azido-substituted 4-anilinoquinazolines for the treatment of hyperproliferative diseases. Schnur, Rodney Caughren; Arnold, Lee Daniel (Pfizer Inc., USA). U.S. US 5747498 A 19980505, 23 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-653786 19960528.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5747498	A	19980505	US 1996-653786	19960528

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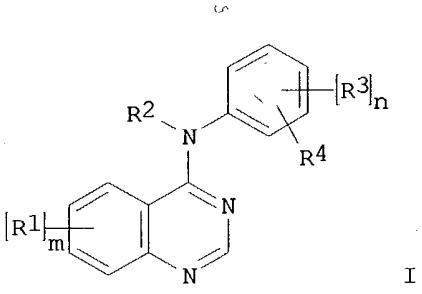

I

AB The title compds. [I; R1 = H, halo, OH, etc.; R2 = H, (un)substituted C1-6 alkyl; R3 = H, halo, OH, etc.; R4 = N3, (un)substituted ethynyl; m = 1-3; n = 1-2] and their salts, useful in the treatment of hyperproliferative diseases such as **cancer**, were prepared Thus, reaction of 4-chloro-6,7-dimethoxyquinazoline with 4-azidoaniline hydrochloride in iPrOH afforded 98% I [R1 = 6,7-Me2; R2, R3 = H; R4 = 4-N3]. Compds. I showed IC50 of 0.0001-30 μM against EGFR kinase.

L3 ANSWER 2 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2002:74864 Document No. 137:134227 Epidermal growth factor receptor tyrosine kinase inhibitors in **cancer** therapy. Adjei, Alex A. (Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA). Drugs of the Future, 26(11), 1087-1092 (English) 2001. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.

AB A review. Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will

summarize current preclin. and clin. knowledge of the small-mol. oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.

L3 ANSWER 3 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2001:935435 Document No. 136:84677 Methods for enhancing antibody-induced cell lysis and treating **cancer**. Weiner, George; Hartmann, Gunther (University of Iowa Research Foundation, USA). PCT Int. Appl. WO 2001097843 A2 20011227, 312 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US20154 20010622. PRIORITY: US 2000-PV213346 20000622.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001097843	A2	20011227	WO 2001-US20154	20010622
	WO 2001097843	A3	20030123		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2003026801	A1	20030206	US 2001-888326	20010622
	EP 1296714	A2	20030402	EP 2001-948684	20010622
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003535907	T2	20031202	JP 2002-503327	20010622

AB The invention relates to methods and products for treating **cancer**. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of **cancer**. The invention also relates to diagnostic methods for screening **cancer** cells.

L3 ANSWER 4 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2001:921398 Document No. 137:87979 Anticancer therapy targeting the ErbB family of receptor tyrosine kinases. Slichenmyer, William J.; Fry, David W. (Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA). Seminars in Oncology, 28(5, Suppl. 16), 67-79 (English) 2001. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..

AB Several agents that target one or more members of the erbB family of receptor tyrosine kinases are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast **cancer** when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities associated with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development.

The orally active tyrosine kinase inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI774, and CI-1033. Evidence to data suggests that the major role for erbB receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

L3 ANSWER 5 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2001:839156 Document No. 136:144494 Lung **cancer**. Evans, Tracey L.; Lynch, Thomas J., Jr. (Massachusetts General Hospital Cancer Center, Boston, MA, 02114, USA). Oncologist, 6(5), 407-414 (English) 2001. CODEN: OCOLF6. ISSN: 1083-7159. Publisher: AlphaMed Press.
AB A review. Is any one combination therapy for metastatic non-small cell lung **cancer** (NSCLC) superior to other regimens for metastatic NSCLC. The answer is "probably number". More than 4000 patients with advanced NSCLC participated in randomized trials presented at the 37th Annual Meeting of the American Society of Clin. Oncol. TAX326 was the only study in which the investigational arm (cisplatin/docetaxel) showed a statistically significant difference in survival compared with the reference standard (cisplatin/vinorelbine). The authors did learn, however, that what is administered may make some difference: cisplatin might be superior to carboplatin, and patients treated with nonplatinum chemotherapy regimens have a trend toward poorer survival than those who receive platinum doublets. Although there is still no clear best regimen for advanced NSCLC, doctors may now know how much chemotherapy to give: a randomized study presented found that four cycles produces as much survival benefit as treating until progression. The most significant abstrs. presented at this year's lung **cancer** session involved the use of novel agents with unique mechanisms of action. The median survival in the large, randomized trials of chemotherapy in advanced NSCLC remains a bleak 9 mo. ISIS 3521, an antisense oligonucleotide that targets protein kinase C, was found to produce a near doubling of survival when combined with carboplatin and paclitaxel. OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, was shown to have impressive single agent activity in the second-line treatment of lung **cancer**. The future of lung **cancer** therapy will involve combining these novel agents with active chemotherapy regimens in an effort to improve outcome. While it appears that a plateau has been reached in what can be accomplished with various combinations of cytotoxic chemotherapy in metastatic NSCLC, in locally-advanced disease new chemotherapy combinations can achieve remarkable results when combined with radiation therapy. The Southwest Oncol. Group presented unprecedented phase II data on the use of cisplatin and etoposide with concurrent radiation therapy followed by consolidation docetaxel in patients with stage IIIB NSCLC.

L3 ANSWER 6 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2001:799777 Document No. 137:27578 A novel approach in the treatment of **cancer**: Targeting the epidermal growth factor receptor. Ciardiello, Fortunato; Tortora, Giampaolo (Cattedra di Oncologia Medica. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli "Federico II,", Naples, 80131, Italy). Clinical Cancer Research, 7(10), 2958-2970 (English) 2001. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.
AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to **cancer** development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in

cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to **cancer** therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in **cancer** patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A number of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

L3 ANSWER 7 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2001:746944 Document No. 136:144431 Targeting the epidermal growth factor receptor: a clinical reality. Baselga, Jose (Vall d'Hebron University Hospital, Barcelona, 08035, Spain). Journal of Clinical Oncology, 19(18, Suppl.), 41s-44s (English) 2001. CODEN: JCONDN. ISSN: 0732-183X. Publisher: Lippincott Williams & Wilkins.

AB A review presents four studies which further establishes the potential of epidermal growth factor (EGF) receptor as a target for **cancer** therapy. A novel EGF receptor tyrosine kinase inhibitor, OSI-774, has antitumor activity against several tumor types. The EGF receptor monoclonal antibody IMC-C225 reverses clin. chemotherapy resistance in colorectal carcinoma. The selective EGT receptor tyrosine kinase inhibitor, ZD1839, prevents activation of HER2 and has antitumor activity alone and in combination with trastuzumab in breast carcinoma cell lines.

L3 ANSWER 8 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2001:713163 Document No. 135:267215 Combined treatment with keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor for reducing EGFR inhibitor-associated epithelial toxicity. Miller, Penelope Elizabeth; Moyer, James Dale (Pfizer Products, Inc., USA; OSI Pharmaceuticals, Inc.). PCT Int. Appl. WO 2001070255 A2 20010927, 24 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US8207 20010315. PRIORITY: US 2000-PV190697 20000320.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001070255	A2	20010927	WO 2001-US8207	20010315
	WO 2001070255	A3	20020228		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002061304	A1	20020523	US 2001-808751	20010315
EP 1276496	A2	20030122	EP 2001-916662	20010315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003527437	T2	20030916	JP 2001-568452	20010315
US 2004071697	A1	20040415	US 2003-458072	20030610

AB Compns. and methods are provided for treating the epithelial toxicity caused by administering to a human **cancer** patient an epidermal growth factor receptor (EGFR) inhibitor. The pharmaceutical composition preferably comprises an EGFR inhibitor and a keratinocyte growth factor (KGF) in a pharmaceutically acceptable carrier. The method of treatment comprises co-administering to the patient a therapeutically effective amount of KGF with the EGFR inhibitor.

L3 ANSWER 9 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2001:696814 Document No. 136:65 Ovarian **cancer**. Seiden, Michael V. (Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, 02114, USA). Oncologist, 6(4), 327-332 (English) 2001. CODEN: OCOLF6. ISSN: 1083-7159. Publisher: AlphaMed Press.

AB A review. Ovarian **cancer** remains the most lethal gynecol. malignancy in women in the United States. Studies from this year's American Society of Clin. Oncol. more clearly defined the role of chemotherapy in women with early stage disease and now suggest that essentially all women with invasive disease should receive chemotherapy that contains carboplatin. Studies in women with advanced disease continue to support the use of carboplatin and paclitaxel in the treatment of women with newly diagnosed disease although early data suggest that carboplatin and docetaxel might be an acceptable alternative. Platinum-resistant disease remains a therapeutic challenge. Small mols. that inhibit the function of the epidermal growth factor receptor, such as OSI-774, and novel classes of chemotherapeutic agents, including the acylfulvene MGI-114 and epothilone B and its analog, BMS247550, all warrant further study in this disease.

L3 ANSWER 10 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2001:359969 Document No. 134:371760 Stable polymorph of N-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, methods of production, and pharmaceutical uses thereof. Connell, Richard D.; Moyer, James D.; Morin, Michael J.; Kajiji, Shama M.; Foster, Barbara A.; Ferrante, Karen J.; Norris, Timothy; Raggon, Jeffrey W.; Silberman, Sandra L. (Osi Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001034574 A1 20010517, 71 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN:

PIXXD2. APPLICATION: WO 2000-US31009 20001109. PRIORITY: US 1999-PV164907 19991111; US 2000-PV193191 20000330; US 2000-PV206420 20000523.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034574	A1	20010517	WO 2000-US31009	20001109
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2000015544	A	20020723	BR 2000-15544	20001109
	EP 1233948	A1	20020828	EP 2000-980346	20001109
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003523949	T2	20030812	JP 2001-536522	20001109
	NZ 518406	A	20040130	NZ 2000-518406	20001109
	ZA 2002003130	A	20030422	ZA 2002-3130	20020419
	NO 2002001910	A	20020701	NO 2002-1910	20020423
	BG 106761	A	20030131	BG 2002-106761	20020531

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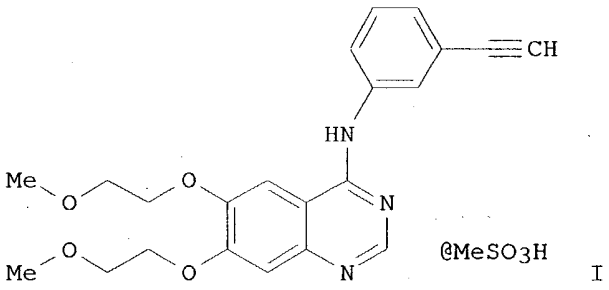

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AB The present invention relates to a stable crystalline form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine-HCl (I) designated the B polymorph, its production in essentially pure form, and its use, e.g., treating hyperproliferative disorders, such as **cancer**. I was prepared and the A form or A + B form mixts. were recrystd. to give polymorph B.

L3 ANSWER 11 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2001:338332 Document No. 134:336209 EGFR tyrosine kinase inhibitors for the prevention of breast **cancer**. Bundred, Nigel James (The University of Manchester, UK). PCT Int. Appl. WO 2001032155 A2 20010510, 38 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL,

PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-GB4190 20001101. PRIORITY: GB 1999-25958 19991102.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001032155	A2	20010510	WO 2000-GB4190	20001101
WO 2001032155	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000015194	A	20020618	BR 2000-15194	20001101
EP 1272188	A2	20030108	EP 2000-973002	20001101
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003513035	T2	20030408	JP 2001-534360	20001101
NO 2002002065	A	20020624	NO 2002-2065	20020430
ZA 2002003431	A	20021209	ZA 2002-3431	20020430

AB An EGFR tyrosine kinase inhibitor (e.g. ZD1839) is used in the manufacture of a medicament for use in (a) reducing the transformation of epithelial cells from a normal to a malignant state in an invasive breast **cancer** free human; and/or (b) reducing the transformation of epithelial cells from an intermediate state, between normal epithelium and malignant invasive epithelium, to a malignant state in an invasive breast **cancer** free human; and/or (c) causing substantial reversion of epithelial tissue back to a normal state from an intermediate state between normal epithelium and malignant invasive epithelium.

L3 ANSWER 12 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2001:160743 Document No. 135:189476 OSI-774 OSI Pharmaceuticals. Norman, Peter (Norman Consulting, Bucks, SL1 8JW, UK). Current Opinion in Investigational Drugs (PharmaPress Ltd.), 2(2), 298-304 (English) 2001. CODEN: COIDAZ. Publisher: PharmaPress Ltd..

AB A review with many refs. OSI-774 (formerly CP-358774), a quinazoline derivative, is an orally active epidermal growth factor receptor (EGFR) inhibitor which was originally under joint development by Pfizer and OSI Pharmaceuticals (formerly Oncogene Science) for the potential treatment of **cancer** (eg, ovarian, non-small cell lung **cancer** (NSCLC) and head and neck). It is being in phase II trials. On 8 Jan. 2001, OSI announced that it had signed an agreement with Roche and Genentech for the global co-development and marketing of OSI-774. The agreement with Genentech covers the United States, that with Roche the rest of the world. In June 2000, OSI gained all development and marketing rights for OSI-774 following Pfizer's merger with Warner-Lambert. In Sept. 2000, Pfizer transferred the IND dossier for OSI-774 to OSI ahead of the time-line agreed in the June 2000 development and marketing rights agreement. The phase II trials will assess OSI-774 both as a single agent and in combination with existing chemotherapy regimens. Phase III trials are expected to be initiated in 2001. In Octoer 2000, Lehman Brothers predicted that OSI-774 would move into pivotal trials in the first half of 2001 and that the drug would be launched in 2003. The analysts also estimated worldwide sales of US $66 million, $85 million and $461 million in 2003, 2004 and 2005, resp., and peak sales in excess of US $500 million.

L3 ANSWER 13 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:81360 Document No. 139:190360 Erlotinib hydrochloride: oncolytic EGF receptor inhibitor. Sorbera, L. A.; Castaner, J.; Silvestre, J. S.; Bayes, M. (Prous Science, Barcelona, 08080, Spain). Drugs of the Future, 27(10), 923-934 (English) 2002. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.
AB A review. The epidermal growth factor receptor (EGFR) is a type 1 receptor tyrosine kinase that is involved in the modulation of cellular differentiation and is overexpressed in many types of human cancers such as lung, pancreatic, ovarian, renal cell, gastric, hepatocellular and breast. Overexpression of EGFR is frequently correlated with increased tumor grade, increased metastatic potential and poor prognosis. Thus, inhibition of EGFR signaling is an attractive therapeutic option for the treatment of **cancer**. One method that can interfere with EGFR is the direct inhibition of EGFR tyrosine kinase activity. Several tyrosine kinase inhibitors have been developed and evaluated over the past 10 yr of which the majority are reversible competitors with ATP for binding to the intracellular catalytic domain of the tyrosine kinase. One such EGFR tyrosine kinase inhibitor that has shown excellent antitumor activity is erlotinib hydrochloride, an oral quinazoline derivative that reversibly and selectively inhibits tyrosine kinase activity.

L3 ANSWER 14 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:57578 Document No. 139:46544 Effects of the epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Ng, Sylvia S. W.; Tsao, Ming-Sound; Nicklee, Trudey; Hedley, David W. (Divisions of Experimental Therapeutics, Ontario Cancer Institute, Medical Biophysics, Princess Margaret Hospital and University of Toronto, Toronto, ON, M5G 2M9, Can.). Molecular Cancer Therapeutics, 1(10), 777-783 (English) 2002. CODEN: MCTOCF. ISSN: 1535-7163. Publisher: American Association for Cancer Research.
AB Pancreatic **cancer** is the fifth leading cause of **cancer** death in North America. Gemcitabine improves the quality of life of patients but fails to significantly reduce mortality. Our laboratory has demonstrated previously that the phosphatidylinositol 3'-kinase inhibitor wortmannin promotes gemcitabine antitumor. The present study examined the effects of the epidermal growth factor receptor (EGFR) inhibitor OSI-774 ("Tarceva") alone and in combination with wortmannin and/or gemcitabine on downstream signaling mols., as well as apoptosis in primary pancreatic **cancer** xenografts implanted orthotopicaly in severely combined immunodeficient mice. Tumors established from two pancreatic **cancer** patients [Ontario **Cancer** Institute Pancreas number (OCIP#) 2 and OCIP#7] were treated with various combinations of the above three drugs and harvested for analyses of the following: the levels of phosphorylated and nonphosphorylated forms of EGFR, protein kinase B (PKB/Akt) and extracellular-regulated kinase (ERK1/2), and the extent of apoptosis using immunofluorescence image anal. and TUNEL assay, resp. OSI-774 alone significantly inhibited phosphorylation of EGFR in both of the primary xenografts. Phosphorylation of pERK decreased in OCIP#2, but not in OCIP#7. No significant effects on pPKB because of OSI-774 were observed in either tumor type. The extent of apoptosis was significantly increased by 2-fold in OCIP#2 tumors treated with gemcitabine and wortmannin in combination; an addnl. 2-fold increase in apoptosis was evident in the presence of OSI-774. Although wortmannin failed to enhance gemcitabine-induced apoptosis in OCIP#7 tumors, the extent of apoptosis was significantly increased with the inclusion of OSI-774 in the combination. Taken together, these findings support the use of OSI-774

plus a phosphatidylinositol 3'-kinase inhibitor in combination with gemcitabine in the treatment of pancreatic **cancer**.

L3 ANSWER 15 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2002:888893 Document No. 137:383800 Chimeric and humanized antibodies and fragments specific to glycosylated EGF receptor for **cancer** diagnosis and therapy. Old, Lloyd J.; Johns, Terrance Grant; Panousis, Con; Scott, Andrew Mark; Renner, Christoph; Ritter, Gerd; Jungbluth, Achim; Stockert, Elisabeth; Collins, Peter; Cavenee, Webster K.; Huang, Huei-Jen; Burgess, Anthony Wilks; Nice, Edouard Collins (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2002092771 A2 20021121, 245 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US15185 20020513. PRIORITY: US 2001-PV290410 20010511; US 2001-PV326019 20010928; US 2001-PV342258 20011221.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002092771	A2	20021121	WO 2002-US15185	20020513
WO 2002092771	A3	20031127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1392359	A2	20040303	EP 2002-739258	20020513

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

AB The invention relates to specific binding members, particularly antibodies and active fragments thereof, which recognize an aberrant post-translationally modified, particularly an aberrant glycosylated form of the EGFR. The binding members, particularly antibodies and fragments thereof, of the invention do not bind to EGFR on normal cells in the absence of amplification of the wild- type gene and are capable of binding the de2-7 EGFR at an epitope which is distinct from the junctional peptide. Antibodies of this type are exemplified by the novel antibody 806 whose VH and VL sequences are illustrated as SEQ ID Nos: 2 and 4 and chimeric antibodies thereof as exemplified by ch806. The antibodies may also be radiolabeled for immunodiagnosis and radioimmunotherapy of cancers, especially brain-resident cancers.

L3 ANSWER 16 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

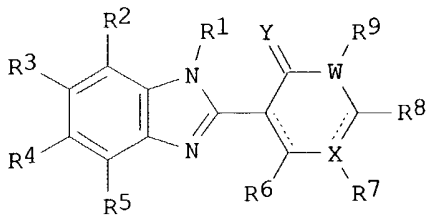
2002:825213 Document No. 138:361940 Targeting the epidermal growth factor receptor for **cancer** therapy. Mendelsohn, John (University of Texas M.D. Anderson Cancer Center, Houston, TX, USA). Journal of Clinical Oncology, 20(18, Suppl.), 1s-13s (English) 2002. CODEN: JCONDN. ISSN: 0732-183X. Publisher: Lippincott Williams & Wilkins.

AB A review. A monoclonal antibody that binds to epidermal growth factor (EGF) receptors and that can block the binding of either EGF or transforming growth factor-alpha (TGF-α) might prevent cell proliferation by inhibiting the signal transduction pathways that depend on activation of the EGF receptor. The author discusses the rationale behind this hypothesis and focus on examples of research findings with three low-mol.-weight, soluble mols. that act on the EGF receptor ZD1839, OSI-774 and C225, including mechanisms of action and results from clin. trials.

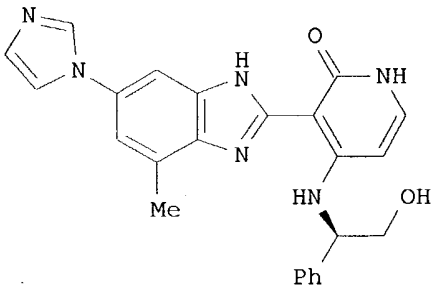
L3 ANSWER 17 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2002:777929 Document No. 137:294954 Preparation of 2-(4-substituted-2-oxo-1,2-dihydropyridin-3-yl)-benzimidazoles as novel tyrosine kinase inhibitors. Wittman, Mark D.; Balasubramanian, Neelakantan; Velaparthi, Upender; Zimmermann, Kurt; Saulnier, Mark G.; Liu, Peiying; Sang, Xiaopeng; Frennesson, David B.; Stoffan, Karen M.; Tarrant, James G. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2002079192 A1 20021010, 249 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US9402 20020326. PRIORITY: US 2001-PV279327 20010328.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002079192	A1	20021010	WO 2002-US9402	20020326
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1381598	A1	20040121	EP 2002-723631	20020326
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	EE 200300475	A	20040216	EE 2003-475	20020326
	NO 2003004308	A	20031126	NO 2003-4308	20030926

GI



I



II

AB The title compds. [I; X = N, C, a bond, etc.; Y = O, S; W = N, C, O, S (if W = O or S, then R9 is absent); R1-R9 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts which inhibit tyrosine kinase enzymes thereby making them useful as anti-**cancer** agents, were prepared Thus, reacting 3-[6-(imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-iodo-1H-pyridin-2-one (preparation given) with (S)-(-)-2-phenylglycinol in the presence of N-methylmorpholine in DMF afforded 52% (S)-II which showed IC50 of 1.0 μM in cytotoxicity assay (HT-29 human colon tumor cell line). 30 Of the exemplified compds. I showed kinase activity of <25μM against one or more of the following kinases CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. The compds. I are also useful for the treatment of other diseases which can be treated by inhibiting tyrosine kinase enzymes.

L3 ANSWER 18 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2002:757182 Document No. 138:313642 Why the epidermal growth factor receptor? The rationale for **cancer** therapy. Baselga, Jose (Medical Oncology Service, Hospital Universitari Vall d'Hebron, Barcelona, Spain). Oncologist, 7(Suppl. 4), 2-8 (English) 2002. CODEN: OCOLF6. ISSN: 1083-7159. Publisher: AlphaMed Press.

AB A review. There is a need for new, selective anticancer agents that differentiate between malignant and non-malignant cells. The benefits of such agents would include a higher therapeutic index and lower toxicity than conventional therapies. Although expressed in non-malignant cells, the epidermal growth factor receptor (EGFR) is highly expressed in a variety of tumors, and its expression correlates with poor response to treatment, disease progression, and poor survival. Evidence for a role for the EGFR in the inhibition and pathogenesis of various cancers has led to the rationale design and development of agents that selectively target this receptor. Activation of the EGFR signaling pathway in **cancer** cells has been linked with increased cell proliferation, angiogenesis, and metastasis, and decreased apoptosis. Preclin. data show that anti-EGFR therapies can inhibit these effects in vitro and in vivo. In addition, preclin. data confirm that many such agents have the potential to increase

the effectiveness of current cytotoxic agents. Following accelerated drug development programs, phase III trials are now under way for a number of EGFR-targeted therapies, including the monoclonal antibody IMC-C225 and the EGFR-tyrosine kinase inhibitors ZD1839 (Iressa) and OSI-774. Thus, the rationale for EGFR-targeted approaches to **cancer** treatment is apparent and now well established, and there is increasing evidence that they may represent a significant contribution to **cancer** therapy.

L3 ANSWER 19 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2002:604225 Document No. 138:162767 EGF signal transduction and its molecular targeted drugs against **cancer**. Sone, Saburo; Yamamoto, Akihiko (Dep. Internal Med. Molecular Therapeutics, Univ. Tokushima Sch. Med., Japan). Saishin Igaku, 57(7), 1712-1717 (Japanese) 2002. CODEN: SAIGAK. ISSN: 0370-8241. Publisher: Saishin Igakusha.
AB A review. The epidermal growth factor receptor (EGFR) and its inhibition in **cancer** therapy is reviewed together with the mechanism related to EGF signal transduction of antitumor agents such as EGFR antibody (C225) and EGFR tyrosine kinase inhibitors (ZD1839, OSI-774, and CI-1033).

L3 ANSWER 20 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2002:521793 Document No. 137:77889 Human antibodies to insulin-like growth factor I receptor. Cohen, Bruce D.; Beebe, Jean; Miller, Penelope E.; Moyer, James D.; Corvalan, Jose R.; Gallo, Michael (Pfizer Inc., USA; Abgenix, Inc.). PCT Int. Appl. WO 2002053596 A2 20020711, 172 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US51113 20011220. PRIORITY: US 2001-PV259927 20010105.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002053596	A2	20020711	WO 2001-US51113	20011220
	WO 2002053596	A3	20040108		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EE 200300318	A	20031015	EE 2003-318	20011220
	EP 1399483	A2	20040324	EP 2001-991634	20011220
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004086503	A1	20040506	US 2002-38591	20020104
	NO 2003003074	A	20030704	NO 2003-3074	20030704

AB The authors disclose the preparation and characterization of antibodies that specifically bind to human insulin-like growth factor I receptor (IGF-IR).

The antibodies were prepared by immunization of XenoMouse with either the extracellular domain of human IGF-IR or with cells transformed for surface expression of the receptor. The isolated antibodies were shown to down-regulate IGF-IR, to prevent its phosphorylation induced by ligand, and to exhibit tumor growth inhibitory activities either alone or in combination with chemotherapeutic agents.

L3 ANSWER 21 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2002:184907 Document No. 136:241643 Exemestane as chemopreventing agent. Di Salle, Enrico; Piscitelli, Gabriella; Massimini, Giorgio; Purandare, Dinesh; Martini, Alessandro; Muggetti, Lorena (Pharmacia & Upjohn S.p.A., Italy; Pharmacia & Upjohn Company). PCT Int. Appl. WO 2002020020 A1 20020314, 33 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP10172 20010831. PRIORITY: US 2000-658052 20000908.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002020020	A1	20020314	WO 2001-EP10172	20010831
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001089865	A5	20020322	AU 2001-89865	20010831
	EP 1317270	A1	20030611	EP 2001-969689	20010831
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001013625	A	20030722	BR 2001-13625	20010831
	JP 2004508334	T2	20040318	JP 2002-524504	20010831
	US 2004024044	A1	20040205	US 2003-363935	20030804

AB The present invention concerns the use of aromatase inhibitor exemestane, either alone or in combination with other therapeutic agents, in the chemoprevention of estrogen dependent **cancer** in mammals, including humans, at increased risk of the disease. Exemestane treatment (4, 20 or 100 mg/kg/wk, IM), started 1 wk after dimethylbenzanthracene (DMBA) exposure (20 mg/rat, PO) and continued for 19 wk, significantly decreased tumor incidence from 85 % in vehicle treated rats to 13.6 % in the 100 mg/kg treated group. Moreover, exemestane at 100 mg/kg reduced significantly the tumor multiplicity, being 2.55 the number of tumors/rat in the control groups vs. 0.27 in the treated group. No signs of toxicity were observed

L3 ANSWER 22 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:335709 Preclinical studies with erlotinib (Tarceva). [Erratum to document cited in CA140:052547]. Akita, Robert W.; Sliwkowski, Mark X. (Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, USA). Seminars in Oncology, 30(6), 826 (English) 2003. CODEN: SOLGAV. ISSN:

0093-7754. Publisher: W. B. Saunders Co..
AB A review. An erratum.

L3 ANSWER 23 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:47341 Document No. 141:33137 Epidermal growth factor receptor-targeted therapy and symptom improvement in non-small cell lung **cancer**. Bonomi, Philip D. (Section of Medical Oncology, Rush University Medical Center, Chicago, IL, 60612, USA). American Journal of Health-System Pharmacy, 60(Suppl. 9), S16-S21 (English) 2003. CODEN: AHSPEK. ISSN: 1079-2082. Publisher: American Society of Health-System Pharmacists.
AB A review. Epidermal growth factor receptor-targeted therapy and symptom improvement in non-small cell lung **cancer** are discussed. Non-small cell lung **cancer** (NSCLC) is a common and frequently incurable disease. Patients with advanced stage IIIB/IV disease, although not candidates for curative resection, can benefit from treatment that prolongs survival, alleviates symptoms, and reduces complications. While incremental advances have occurred with the use of chemotherapy and radiation therapy, the benefits have been largely palliative. Moreover, the adverse events associated with these therapies may undermine the treatment goal by replacing disease-related symptoms with treatment-related adverse events. Thus, novel, more targeted approaches are needed. Increased understanding of cellular and mol. biol. has resulted in the development of treatments that selectively target key regulatory pathways and mols. involved in cell growth and metastasis. Gefitinib is one member of a new class of targeted anticancer agents known as tyrosine kinase inhibitors with activity against NSCLC. In clin. trials, gefitinib has produced responses in patients with relapsed or refractory NSCLC, reduced disease-related symptoms, and has been associated with improvements in quality of life. Such targeted therapy may have a significant impact on the treatment of patients with NSCLC.

L3 ANSWER 24 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:31795 Document No. 140:70157 Epidermal growth factor receptor tyrosine kinase inhibitors in late stage clinical trials. Ciardiello, Fortunato; De Vita, Ferdinando; Orditura, Michele; De Placido, Sabino; Tortora, Giampaolo (Cattedra di Oncologia Medica, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale 'F Magrassi e A Lanzara, Seconda Universita degli Studi di Napoli, Naples, Italy). Expert Opinion on Emerging Drugs, 8(2), 501-514 (English) 2003. CODEN: EOEDA3. Publisher: Ashley Publications Ltd..
AB A review. The epidermal growth factor receptor (EGFR) is a cell membrane receptor that plays a key role in **cancer** development and progression. Ligand-activated EGFR-dependent signaling is involved in cell proliferation, apoptosis, angiogenesis and metastatic spread. Targeting the EGFR, therefore, represents a promising mol. approach in **cancer** treatment. Several anti-EGFR agents are in clin. development. Three drugs are currently in Phase II and III development as single agents, or in combination with other anticancer modalities: IMC-225 (cetuximab/Erbitux; ImClone), a chimeric human-mouse monoclonal IgG1 antibody, which blocks ligand binding and functional activation of the EGFR; OSI-774 (erlotinib/Tarceva; Genentech/OSI/Roch) and ZD1839 (gefitinib/Iressa; AstraZeneca), two small mol. EGFR-selective inhibitors of tyrosine kinase enzymic activity, which prevent EGFR autophosphorylation and activation. Iressa is the first EGFR-targeting agent to be registered as an anticancer drug in Japan, in Australia and in the US for the third-line treatment of chemoresistant non-small cell lung **cancer** (NSCLC) patients. This review will focus on the preclin. background and on the results from the first series of clin. trials with

these drugs. Furthermore, continuing clin. trials and a series of open clin. issues for the development of optimal strategies of using EGFR-targeting agents will be discussed.

L3 ANSWER 25 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:971730 Document No. 140:27844 Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors. Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-Yu; James, Ray A.; Bishop, W. Robert; Wang, James J. S.; Desai, Jagdish A. (USA). U.S. Pat. Appl. Publ. US 2003229099 A1 20031211, 519 pp., Cont.-in-part of U.S. Pat. Appl. 2002 198,216. (English). CODEN: USXXCO. APPLICATION: US 2002-85896 20020227. PRIORITY: US 2000-PV229183 20000830; US 2001-940811 20010828.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003229099	A1	20031211	US 2002-85896	20020227
	US 2002198216	A1	20021226	US 2001-940811	20010828
	US 2004122018	A1	20040624	US 2002-325896	20021219
	US 2004122018	A1	20040624	US 2002-325896	20021219
	US 2004122018	A1	20040624	US 2002-325896	20021219
	WO 2003072549	A1	20030904	WO 2003-US5479	20030225

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; one of a, b, d, e = N, N:O; remaining a, b, d, e = C (wherein each C atom has an R1 or R2 bound to said carbon); or each a, b, d, e = C (wherein each C atom has an R1 or R2); R1-R4 = H, halo, CF3, alkoxy, etc.; R5-R7, R9 = H, CF3, alkyl, aryl, etc.; R8 = H, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, etc.; dotted line = single or double bond; X = N, CH; A, B = (un)substituted CH, CH2], their stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs which are useful for inhibiting farnesyl protein transferase, were prepared E.g., a multi-step synthesis of II, was given. The compds. I have an FTP IC50 in the range of 0.05 nM to 100 nM. Also disclosed are pharmaceutical compns. comprising title compds. I as well as methods of using them to treat proliferative diseases such as **cancer.**

L3 ANSWER 26 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:931201 Document No. 140:13024 EGF receptor antagonists in the treatment of gastric **cancer.** Luber, Birgit; Fuchs, Margit Roswitha; Hoefler, Heinz; Fend, Falko; Gamboa-Dominguez, Armando (Technische

Universitaet Muenchen, Germany). PCT Int. Appl. WO 2003097086 A2 20031127, 153 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP5057 20030514. PRIORITY: US 2002-PV380285 20020515; EP 2003-4524 20030228.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003097086	A2	20031127	WO 2003-EP5057	20030514
	WO 2003097086	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AB The invention relates to a use of (an) EGF receptor antagonist(s)/inhibitor(s) for the preparation of a pharmaceutical composition for the prevention, amelioration or treatment of gastric carcinomas, preferably for the prevention, amelioration or treatment of diffuse gastric carcinomas. Furthermore, the invention provides for a method for treating or for preventing gastric carcinomas, in particular diffuse gastric carcinomas comprising the administration of at least one EGF receptor antagonist/inhibitor to a subject in need of such a treatment or prevention.

L3 ANSWER 27 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:825337 Document No. 139:345184 Development of the epidermal growth factor receptor inhibitor Tarceva (OSI-774). Gruenwald, Viktor; Hidalgo, Manuel (The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, 21231-1000, USA). Advances in Experimental Medicine and Biology, 532(New Trends in Cancer for the 21st Century), 235-246 (English) 2003. CODEN: AEMBAP. ISSN: 0065-2598. Publisher: Kluwer Academic/Plenum Publishers.

AB A review. The epidermal growth factor receptor (EGFR) is a transmembrane receptor involved in the regulation of a complex array of essential biol. processes such as cell proliferation and survival. Dysregulation of EGFR signaling network has been frequently reported in multiple human cancers and has been associated with the processes of tumor development, growth, proliferation, metastasis and angiogenesis. Inhibition of the EGFR was associated with antitumor effects in preclin. models. On the bases of these data, therapeutics targeting the EGFR were explore in clin. trials. Tarceva (OSI-774, OSI Pharmaceuticals, Uniondale, NY) is a small mol. selective inhibitor of the EGFR tyrosine kinase (TK). In preclin. studies, Tarceva inhibited the phosphorylation of the EGFR in a dose and concentration dependent manner resulting in cell cycle arrest and induction of apoptosis. In in vivo studies, the agent caused tumor growth inhibition

and shoved synergistic effects when combined with conventional chemotherapy. Subsequent single agent phase I studies and phase I studies in combination with chemotherapy demonstrated that the agent has a good safety profile and induced tumor growth inhibition in a substantial number of patients with a variety of different solid tumor. Preliminary report from phase II studies confirmed the excellent tolerability of Tarceva as well as showed encouraging preliminary activity. Phase III studies have either been completed or are ongoing in several tumor types such as lung **cancer** and pancreatic **cancer**. In summary, Tarceva is a novel inhibitor of the EGFR TK which has shown promising activity in initial studies and is currently undergoing full development as an anticancer drug.

L3 ANSWER 28 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:737931 Document No. 139:255332 Method for selecting antitumor drug sensitivity-determining factors and method for predicting antitumor drug sensitivity using the selected factors. Aoki, Yuko; Hasegawa, Kiyoshi; Ishii, Nobuya; Mori, Kazushige (F. Hoffmann-La Roche A.-G., Switz.). PCT Int. Appl. WO 2003076660 A1 20030918, 81 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-JP2354 20020313.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003076660	A1	20030918	WO 2002-JP2354	20020313

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AB Based on drug sensitivity data and extensive gene expression data, a model was constructed by multivariate anal. with the partial least squares method type 1. Further, the model was optimized using modeling power and genetic algorithm. Thereby, the degree of contribution of the resp. genes to drug sensitivity was determined to select genes with a high degree of contribution. In addition, the levels of gene expression in specimens were analyzed, and then the drug sensitivity was predicted based on the model. The predicted values agreed well with those drug sensitivity values determined exptl. The drug sensitivity-predicting method provided by the present invention enables assessment of the effectiveness of a drug prior to administration using small quantities of specimens associated with diseases such as **cancer**. Since this enables the selection of the most suitable drug for each patient, the present invention is very useful in improving a patient's quality of life (QOL).

L3 ANSWER 29 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:695035 Document No. 140:104240 Epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung **cancer**.

Fukuoka, Masahiro; Nakagawa, Kazuhiko (Department of Medical Oncology, Kinki University School of Medicine, Osaka, 589-8511, Japan). Biotherapy (Tokyo, Japan), 17(4), 346-351 (Japanese) 2003. CODEN: BITPE9. ISSN: 0914-2223. Publisher: Gan to Kagaku Ryohosha.

AB A review. EGFR tyrosine kinase inhibitors (EGFR-TKIs) are currently being developed as a **cancer** therapeutic agent. EGFR-TKI which has been performed clin. trials in non-small cell lung **cancer** (NSCLC) includes gefitinib (Iressa) and erlonitib (Tarceva). Two randomized double blind phase II trials of single agent gefitinib (IDEAL 1 and 2) have shown significant activity and tolerability in patients with previously treated NSCLC. Response rates were 18.4% on 250 mg/day and 19% on 500 mg/day in IDEAL 1, and 11.0% on 250 mg/day and 9.0% on 500 mg/day in IDEAL 2. Drug-related adverse events (AEs) in both trials were generally mild (grade 1/2), consisting mainly of skin reactions and diarrhea. Fewer patients on 250 mg/day gefitinib experienced drug-related grade 3 or 4 AEs compared with 500 mg/day. Severe acute interstitial lung disease does occur in association with gefitinib treatment. Phase III studies comparing standard chemotherapy (carboplatin/taxol and cisplatin/gemcitabine) and gefitinib with placebo have been conducted in patients with previously untreated NSCLC. These trials have shown that any differences are not observed between the gefitinib and the placebo groups. A single agent phase II trial of erlotinib has been conducted to assess the efficacy and safety of erlotinib in 57 patients with EGFR-pos. NSCLC who had failed prior platinum-based chemotherapy. All patients received erlotinib as a 150 mg/day orally for a maximum of 52 wk, or until disease progression or unmanageable toxicity. Of the 57 patients, two achieved a CR and five had a PR, resulting in an overall RR of 12.3%. The most common rash and/or diarrhea occurred as single events or concurrently in 90% of the patients. Grade 3 events occurring in 2 patients (4%) each were: dysphagia, pruritus, fatigue, and dyspnea. Only one patient had grade 3 diarrhea. In conclusion, single agent activity of gefitinib or erlotinib in terms of response and survival data, as well as the lack of severe toxicities commonly associated with cytotoxic chemotherapy, indicate that the EGFR-TKI has a favorable risk-to-benefit ratio for the treatment of patients with advanced NSCLC whose disease has progressed or relapsed following platinum-based chemotherapy.

L3 ANSWER 30 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:682016 Document No. 140:209642 Molecular target-based **cancer** therapy: tyrosine kinase inhibitors. Tamura, Kenji; Fukuoka, Masahiro (Department of Medical Oncology, Kinki University School of Medicine, Osaka, 589-8511, Japan). International Journal of Clinical Oncology, 8(4), 207-211 (English) 2003. CODEN: IJCOF6. ISSN: 1341-9625. Publisher: Springer-Verlag Tokyo.

AB A review. Improved understanding of tumor biol. has led to the identification of numerous growth factors that are involved in malignant transformation and tumor progression. Many of these factors induce cellular responses through receptors with intrinsic tyrosine kinase (TK) activity. Therefore, inhibiting the activity of TK receptors is one of the ways to effectively block the disordered proliferation of **cancer** that arises from these pathways. The human epidermal growth factor receptor (HER) family is overexpressed or dysfunctional in many human malignancies. Therefore, these receptors have been identified as targets for **cancer** therapy. Several agents have been developed that reversibly or irreversibly inhibit one, two, or all of the HER receptors. Iressa and Tarceva are HER1-specific TK inhibitors that are in advanced development. The large phase II study of Iressa (IDEAL1) in patients with non-small-cell lung **cancer** (NSCLC) in whom

previous platinum-based therapy has failed, found that the median survival time (MST) was 7.6 mo, which was no less than that with Docetaxel treatment. Other dual or pan-HER, reversible or irreversible, TK inhibitors are being investigated in phase I trials. Early data show that they are generally well tolerated and have provided evidence of against activity tumors. HER-TK inhibitors are likely to have a substantial impact on the treatment of **cancer** patients.

L3 ANSWER 31 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:640503 Document No. 140:52547 Preclinical studies with erlotinib (Tarceva). Akita, Robert W.; Sliwkowski, Mark X. (Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, USA). Seminars in Oncology, 30(3, Suppl. 7), 15-24 (English) 2003. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..
AB A review. Erlotinib HCl (Tarceva; Genentech, Inc, South San Francisco, CA) is an orally available, highly selective, reversible inhibitor of epidermal growth factor receptor (HER1/EGFR) tyrosine kinase. Inhibition of tyrosine kinase activity prevents HER1/EGFR phosphorylation, the associated downstream signaling events, and may block tumorigenesis mediated by inappropriate HER1/EGFR signaling. In vitro and in vivo studies show that erlotinib has activity against human colorectal, head and neck, non-small cell lung, and pancreatic tumor cells. Recent preclin. studies suggest that erlotinib may also have activity against tumors that are dependent on HER2 activation for growth and/or survival. Preclin. studies have addressed the feasibility of using erlotinib in combination with various chemotherapeutic agents, radiotherapy, and targeted agents. Combining agents that have different mechanisms of action has the potential to improve efficacy and inhibit the development of resistance. For example, in preclin. studies, combining erlotinib with cisplatin, doxorubicin, gemcitabine, or low-dose paclitaxel has an additive effect on antitumor activity with no increase in toxicity. Preclin. data provide a strong rationale for investigating erlotinib in the clin. setting. However, addnl. studies are required to gain further insights into the processes that regulate or influence the antitumor activity of erlotinib.

L3 ANSWER 32 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:613804 Document No. 140:52925 The biological and biochemical effects of CP-654577, a selective erbB2 kinase inhibitor, on human breast **cancer** cells. Barbacci, E. Gabriella; Pustilnik, Leslie R.; Rossi, Ann Marie K.; Emerson, Erling; Miller, Penny E.; Boscoe, Brian P.; Cox, Eric D.; Iwata, Kenneth K.; Jani, Jitesh P.; Provoncha, Kathleen; Kath, John C.; Liu, Zhengyu; Moyer, James D. (Pfizer Global Research and Development, Groton, CT, 06340, USA). Cancer Research, 63(15), 4450-4459 (English) 2003. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.
AB Aberrant expression or activity of epidermal growth factor receptor (EGFr) or the closely related p185erbB2 can promote cell proliferation and survival and thereby contribute to tumorigenesis. Specific antibodies and low mol.-weight tyrosine kinase inhibitors of both proteins are in clin. trials for **cancer** treatment. CP-654577 is a potent inhibitor selective for p185erbB2, relative to EGFr tyrosine kinase, and selectively reduces erbB2 autophosphorylation in intact cells. Treatment of SKBr3 human breast **cancer** cells with CP-654577 reduces the levels of the activated form of mitogen-activated protein kinase, increases the levels of cyclin-dependent kinase inhibitor p27kip1 and reduces expression of cyclins D and E. These biochem. changes result in a reduced level of phosphorylated retinoblastoma protein and an inhibition of cell-cycle progression at G1. Apoptosis is triggered in both SKBr3 and another high

erbB2-expressing cell line, BT474, by exposure to 1 μM CP-654577, but this effect is not observed in MCF7 cells that express low erbB2. Levels of activated Akt, an important pos. regulator of cell survival, are reduced within 2 h of exposure to 250 nM CP-654577, and this may contribute to the increased apoptosis. These biochem. effects are distinct from those produced by Tarceva, a selective EGFr inhibitor. The antitumor activity of CP-654577 was investigated in athymic mice bearing s.c. tumors from Fischer rat embryo fibroblasts transfected with erbB2. CP-654577 produced a dose-dependent reduction of p185erbB2 autophosphorylation and inhibited the growth of these tumors. CP-654577 warrants further evaluation in tumors with high expression of p185erbB2 and may differ from selective EGFr inhibitors or nonselective dual EGFr/erbB2 inhibitors in efficacy and therapeutic index.

L3 ANSWER 33 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:553651 Document No. 139:190525 Development of the epidermal growth factor receptor inhibitor OSI-774. Grunwald, Viktor; Hidalgo, Manuel (The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA). Seminars in Oncology, 30(3, Suppl. 6), 23-31 (English) 2003. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..
AB A review. The epidermal growth factor receptor (EGFR) is a transmembrane receptor involved in the regulation of a complex array of essential biol. processes such as cell proliferation and survival. Dysregulation of the EGFR signaling network has been frequently reported in multiple human cancers and has been associated with the processes of tumor development, growth, proliferation, metastasis, and angiogenesis. Inhibition of the EGFR was associated with antitumor effects in preclin. models. On the basis of these data, therapeutics targeting the EGFR were explored in clin. trials. OSI-774 is a small-mol. selective inhibitor of the EGFR tyrosine kinase. In.preclin. studies, OSI-774 inhibited the phosphorylation of the EGFR in a dose-dependent and concentration-dependent manner resulting in cell cycle arrest and induction of apoptosis. In in vivo studies, this agent caused tumor growth inhibition and showed synergistic effects when combined with conventional chemotherapy. Subsequent single-agent phase I studies and phase I, studies in combination with chemotherapy showed that the agent has a good safety profile and induced tumor growth inhibition in a substantial number of patients with a variety of different solid tumors. Preliminary reports from phase II studies confirmed the excellent tolerability of OSI-774 and showed encouraging preliminary activity. Phase III studies have either been completed or are ongoing in several tumor types such as lung **cancer** and pancreatic **cancer**. In summary, OSI-774 is a novel inhibitor of the EGFR tyrosine kinase that has shown promising activity in initial studies and is currently undergoing full development as an anticancer drug.

L3 ANSWER 34 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:543288 Document No. 139:190493 Erlotinib (Tarceva): a promising drug targeting epidermal growth factor receptor tyrosine kinase. Bulgaru, Anca M.; Mani, Sridhar; Goel, Sanjay; Perez-Soler, Roman (Department of Oncology, Montefiore Medical Center, Bronx, NY, 10467, USA). Expert Review of Anticancer Therapy, 3(3), 269-279 (English) 2003. CODEN: ERATBJ. ISSN: 1473-7140. Publisher: Future Drugs Ltd..
AB A review. Overexpression of the epidermal growth factor receptor (EGFR) is correlated with a poor prognosis in several human malignancies. In addition, cancers overexpressing EGFR respond poorly to both chemotherapy and radiation therapy. Therefore, EGFR is a viable target for **cancer** therapy. This review will address how EGFR blockade modulates signal transduction, leading to alterations in the cell cycle progression with

secondary inhibition of proliferation and differentiation of **cancer** cells. As a prototypical example, edofinib (Tarceva), a reversible EGFR tyrosine kinase inhibitor will be discussed. This drug has demonstrated promising antitumor activity in Phase II trials in several solid tumors and definitive Phase III studies to demonstrate clin. benefit have completed accrual.

L3 ANSWER 35 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:528791 Document No. 140:52880 Pharmacodynamic Evaluation of the Epidermal Growth Factor Receptor Inhibitor OSI-774 in Human Epidermis of **Cancer** Patients. Malik, Shazli N.; Siu, Lillian L.; Rowinsky, Eric K.; de Graffenried, Linda; Hammond, Lisa A.; Rizzo, Jinee; Bacus, Sarah; Brattain, Michael G.; Kreisberg, Jeffrey I.; Hidalgo, Manuel (The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA). Clinical Cancer Research, 9(7), 2478-2486 (English) 2003. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.

AB BACKGROUND: OSI-774 is an inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK) currently in clin. development. In preclin. models, the antitumor activity of OSI-774 was directly related to its ability to inhibit the EGFR-TK. On the basis of these data, we hypothesized that inhibition of the EGFR-TK will be required for this agent to be effective in the clinic. This study evaluated the pharmacodynamic effects of OSI-774 in normal skin tissues collected from patients treated with the agent in a Phase I study. METHODS: Patients with advanced **cancer** who were treated in a Phase I study of OSI-774 underwent a biopsy of normal skin epidermis at baseline and after the last dose of drug in the first course of treatment. The expression and activation of the EGFR, downstream signaling extracytoplasmatic-regulated kinase (Erk), and cell cycle regulator p27 were determined in paraffin-embedded skin tissues using an immunohistochem. method (IHC). The IHC data were analyzed using both a semiquant. scoring system and an automatic absorbance quant. IHC method. The number of cells with nuclear staining of p27 per 500 cells was determined Plasma samples were collected to quantitate OSI-774 plasma concns. RESULTS: A total of 56 skin specimens was collected from 28 patients treated with OSI-774 at doses ranging from 25 to 200 mg/day. There was a significant decrease in phospho-EGFR (Tyr 1173) expression as determined semiquant. with OSI-774 treatment [2.75 ± 0.51 (mean ± SD) pretreatment vs. 2.36 ± 0.76 after treatment, pair comparison P = 0.01]. The quant. ratio [(phospho-EGFR/EGFR) x 100] of phospho-EGFR (Tyr1173) decreased from 64.16 ± 36.58 pretreatment to 48.87 ± 35.37 post-treatment (pair comparison, P = 0.02). No significant differences were observed in phospho-Erk (Thr202/Tyr204) expression. The mean number of cells with nuclear staining for p27 increased from 185 ± 101 (mean ± SD) pretreatment to 253 ± 111 post-treatment (pair comparison P = 0.02). A total of 12 (42.8%), 7 (25%), and 14 (50%) patients had >25% variation in the ratio of phospho-EGFR (Tyr1173), phospho-Erk (Thr202/Tyr204), and p27 expression, resp. Only changes in p27 expression were related to the administered dose of OSI-774. CONCLUSIONS: OSI-774 exerted pharmacodynamic effects in skin tissues of 30-50% of patients treated with the agent. Up-regulation of p27, which is a downstream effect of EGFR inhibition, was dose related. Although there was a significant decrement in phospho-EGFR (Tyr1173), it was not related to the administered dose of OSI-774. On the basis of these findings and the relatively simple and reliable method to measure p27 expression, this biomarker appears to be the most promising and is being evaluated in Phase II studies as a predictor of clin. outcome.

L3 ANSWER 36 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:454174 Document No. 139:30787 Methods of treating **cancer** using a farnesyl protein transferase (FPT) inhibitor and antineoplastic agents. Cutler, David L.; Meyers, Michael L.; Baum, Charles; Zaknoen, Sara L. (Schering Corporation, USA). PCT Int. Appl. WO 2003047697 A2 20030612, 53 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US37954 20021125. PRIORITY: US 2001-PV334411 20011130.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003047697	A2	20030612	WO 2002-US37954	20021125
	WO 2003047697	A3	20031030		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003185831	A1	20031002	US 2002-303259	20021125
	EP 1448268	A2	20040825	EP 2002-789901	20021125
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

AB The invention discloses a use of an FPT inhibitor for the manufacture of a medicament for the treatment of **cancer**. The treatment comprises administering a therapeutically effective amount of the medicament and therapeutically effective amts. of one or more antineoplastic agents. The cancers treated include non-small cell lung **cancer**, chronic myeloid leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma and multiple myeloma.

L3 ANSWER 37 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:442265 Document No. 139:373873 Target-based agents against ErbB receptors and their ligands: A novel approach to **cancer** treatment. Normanno, N.; Bianco, C.; De Luca, A.; Maiello, M. R.; Salomon, D. S. (Division of Hematological Oncology and Department of Experimental Oncology, INT-Fondazione Pascale, Naples, 80131, Italy). Endocrine-Related Cancer, 10(1), 1-21 (English) 2003. CODEN: ERCAE9. ISSN: 1351-0088. Publisher: Society for Endocrinology.
AB A review. The ErbB receptors and their cognate ligands that belong to the epidermal growth factor (EGF) family of peptides are involved in the pathogenesis of different types of carcinomas. In fact, the ErbB receptors and the EGF-like growth factors are frequently expressed in human tumors. These proteins form a complex system that regulates the proliferation and the survival of **cancer** cells. Therefore, ErbB receptors and their ligands might represent suitable targets for novel therapeutic approaches in human carcinomas. In this regard, different target-based agents that are directed against the ErbB receptors have been developed in the past two decades. One of these compds., the humanized

anti-ErbB-2 monoclonal antibody trastuzumab has been approved for the treatment of patients with metastatic breast **cancer**. The anti-EGF receptor (EGFR) antibody C225, as well as EGFR tyrosine kinase inhibitors ZD1839 and OSI-774 are currently in phase III clin. development. Several other ErbB tyrosine kinase inhibitors are in phase I/II studies. These compds. have generally been shown to have an acceptable toxicity profile and promising antitumor activity in heavily pretreated patients. The mechanisms of action of these compds., as well as the potential therapeutic strategies to improve their efficacy are discussed in this review with particular regard to the combinations of anti-ErbB agents with cytotoxic drugs, or combinations of different ErbB-targeting agents.

L3 ANSWER 38 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:417621 Document No. 139:7174 Method for identification of tumor targeting enzymes for design of compounds which generate anticancer substances. Ishitsuka, Hideo; Okabe, Hisafumi; Shimma, Nobuo; Tsukuda, Takuo; Umeda, Isao (F. Hoffmann-La Roche A.-G., Switz.). PCT Int. Appl. WO 2003043631 A2 20030530, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-EP12911 20021118. PRIORITY: EP 2001-127401 20011123; EP 2001-130245 20011219; EP 2002-5298 20020312.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003043631	A2	20030530	WO 2002-EP12911	20021118
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003138864	A1	20030724	US 2002-301460	20021121

AB The invention relates to a method for the identification of enzymes that are preferentially expressed in certain tumor tissue as compared with rapidly growing normal cells or tissue and the use of the enzymes to design compds. which generate active anticancer substances selectively in tumor tissue. Compds. X-Y-Q [X is a pro-moiety that is designed to generate an active anticancer substance (Q-Y-H) selectively in tumors by the enzymes; Q-Y- is a radical derived from the active anticancer substance in which Y is O, S or N] and their pharmaceutically-acceptable salts are claimed. Thus, 13α-[(2R,3S)-2-[(5S)-[5-[(2S)-(2-aminopropionyl)amino]-5-hydroxycarbonyl]pentanoyloxy]-3-(benzoylamino)-3-phenylpropionyloxy]-2a-(benzyloxy)-4a,10β-diacetoxy-1β,7β-dihydroxy-5β,20-epoxytax-1-en-9-one formic acid salt (I) was prepared by reaction of taxol with (2S)-2-[(2S)-2-(benzyloxycarbonylamino)-3-phenylpropionylamino]hexanedioic acid 1-benzyl ester. Compound I showed cytotoxicity IC50 = 51 nM after 24 h against human colon **cancer**

cell line HCT116.

L3 ANSWER 39 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:355612 Document No. 138:362649 Treatment of **cancer** with anti-ErbB2 antibodies. Sliwkowski, Mark X. (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2003086924 A1 20030508, 56 pp., Cont.-in-part of U.S. Ser. No. 602,812. (English). CODEN: USXXCO. APPLICATION: US 2002-268501 20021010. PRIORITY: US 1999-PV141316 19990625; US 2000-602812 20000623.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003086924	A1	20030508	US 2002-268501	20021010
	US 2004013667	A1	20040122	US 2003-608626	20030627

AB The present application describes methods for treating **cancer** with anti-ErbB2 antibodies, such as anti-ErbB2 antibodies that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal antibody 2C4 was effective in inhibiting breast **cancer** tumor growth in MCF7 xenografts.

L3 ANSWER 40 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:309404 Document No. 139:143909 Enzymatic nucleic acid treatment of diseases or conditions related to levels of epidermal growth factor receptors. Akhtar, Saghir; McSwiggen, James (Kuwait). U.S. Pat. Appl. Publ. US 2003073207 A1 20030417, 199 pp., Cont.-in-part of U.S. Ser. No. 401,063. (English). CODEN: USXXCO. APPLICATION: US 2001-XA848754 20010503. PRIORITY: US 1997-PV36476 19970131; US 1997-985162 19971204; US 1999-401063 19990922.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003073207	A1	20030417	US 2001-848754	20010503
	US 6057156	A	20000502	US 1997-985162	19971204
	AU 9851819	A1	19980611	AU 1998-51819	19980112
	AU 729657	B2	20010208		
	AU 9939188	A1	19990916	AU 1999-39188	19990713
	US 6623962	B1	20030923	US 1999-401063	19990922
	AU 769175	B2	20040115	AU 2000-56616	20000911

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, allozymes and antisense, which modulate the expression of epidermal growth factor receptor genes. The sequence of human epidermal growth factor receptor (EGFR) gene is screened for accessible sites using a computer-folding algorithm. Regions of the RNA that do not form secondary folding structures and contain potential enzymic nucleic acid mol. and/or antisense binding/cleavage sites are identified and used to design the complementary regions of the antisense and enzymic nucleic acid mols. Two human cell lines, A549 lung carcinoma cells and SKOV3 ovarian carcinoma cells known to express medium to high levels of EGFR protein, are used in anti-proliferation assays for nucleic acid screening. The invention designs, synthesizes and tests nucleic acid mols. that target both EGFR and HER2 RNA in cell proliferation and RNA reduction assays for potential use in treating **cancer**. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L3 ANSWER 41 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:300894 Document No. 138:297633 Method of treatment of thyroid **cancer**. Fagin, James Alexander (The University of Cincinnati, USA). PCT Int. Appl. WO 2003030908 A2 20030417, 20 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US32195 20021008. PRIORITY: US 2001-PV327880 20011009.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003030908	A2	20030417	WO 2002-US32195	20021008
	WO 2003030908	A3	20031106		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	EP 1435959	A2	20040714	EP 2002-778482	20021008

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

AB The invention relates to a method of treating a warm-blooded animal, especially a human, having a disease which is mediated or characterized by mutations in the RET gene, or thyroid **cancer**, especially thyroid **cancer** harboring RET mutations, comprising administering to said animal a therapeutically effective amount of a compound which decreases the activity of the epidermal growth factor (EGF), especially a compound as defined herein.

L3 ANSWER 42 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:300541 Document No. 138:281108 Enzymatic nucleic acid treatment of diseases or conditions related to levels of epidermal growth factor receptors. Akhtar, Saghir; McSwiggen, James (Kuwait). U.S. Pat. Appl. Publ. US 2003073207 A1 20030417, 199 pp., Cont.-in-part of U.S. Ser. No. 401,063. (English). CODEN: USXXCO. APPLICATION: US 2001-848754 20010503. PRIORITY: US 1997-PV36476 19970131; US 1997-985162 19971204; US 1999-401063 19990922.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003073207	A1	20030417	US 2001-848754	20010503
	US 6057156	A	20000502	US 1997-985162	19971204
	AU 9851819	A1	19980611	AU 1998-51819	19980112
	AU 729657	B2	20010208		
	AU 9939188	A1	19990916	AU 1999-39188	19990713
	US 6623962	B1	20030923	US 1999-401063	19990922
	AU 769175	B2	20040115	AU 2000-56616	20000911
	US 2003064945	A1	20030403	US 2001-916466	20010725
	US 2003186909	A1	20031002	US 2002-277494	20021021

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, allozymes and antisense, which modulate the expression of epidermal growth factor receptor genes. The sequence of human epidermal growth factor receptor (EGFR) gene is screened for accessible sites using a computer-folding algorithm. Regions of the RNA that do not form secondary

folding structures and contain potential enzymic nucleic acid mol. and/or antisense binding/cleavage sites are identified and used to design the complementary regions of the antisense and enzymic nucleic acid mols. Two human cell lines, A549 lung carcinoma cells and SKOV3 ovarian carcinoma cells known to express medium to high levels of EGFR protein, are used in anti-proliferation assays for nucleic acid screening. The invention designs, synthesizes and tests nucleic acid mols. that target both EGFR and HER2 RNA in cell proliferation and RNA reduction assays for potential use in treating **cancer**. [This abstract record is one of 2 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L3 ANSWER 43 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:252600 Document No. 139:275243 Epidermal growth factor receptor as a therapeutic target in colorectal **cancer**. Cohen, Roger B. (Fox Chase Cancer Center, Philadelphia, PA, USA). Clinical Colorectal Cancer, 2(4), 246-251 (English) 2003. CODEN: CCCLCF. ISSN: 1533-0028. Publisher: Cancer Information Group.
AB A review. The epidermal growth factor receptor (EGFR) is widely expressed in advanced colorectal cancers (CRCs), and higher levels of EGFR are inversely related to survival in these patients. Two general strategies have been used to block EGFR signaling: preventing ligand binding with anti-EGFR monoclonal antibodies (eg, cetuximab and ABX-EGF) and inhibiting its intrinsic tyrosine kinase with small mols. (eg, gefitinib [Iressa] and erlotinib [OSI-774,Tarceva]). Phase II trials of cetuximab suggest that it might be an effective treatment option alone or in combination with standard therapies as first- or second-line therapy. Phase I studies evaluating other EGFR inhibitors in patients with CRC have been reported. The inclusion of anti-EGFR therapies into standard treatment is the subject of current clin. trials.

L3 ANSWER 44 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2003:211937 Document No. 139:78226 Signal transduction-directed **cancer** treatments. Sausville, Edward A.; Elsayed, Yusri; Monga, Manish; Kim, George (Developmental Therapeutics Program, National Cancer Institute, Rockville, MD, 20852, USA). Annual Review of Pharmacology and Toxicology, 43, 199-231 (English) 2003. CODEN: ARPTDI. ISSN: 0362-1642. Publisher: Annual Reviews Inc..
AB A review. The pathogenic mechanisms giving rise to **cancer** frequently involve altered signal transduction pathways. Therefore therapeutic agents that directly address signal transduction mols. are being explored as **cancer** treatments. Inhibitors of protein tyrosine and threonine kinases including STI-571, ZD-1839, OSI-774, and flavopiridol are ATP-site antagonists that have completed initial phase I and phase II evaluations. Herceptin and C225 are monoclonal antibodies also directed against signaling targets. Numerous other kinase antagonists are in clin. evaluation, including UCN-01 and PD184352. Alternative strategies to downmodulate kinase-driven signaling include 17-allyl-amino-17-demethoxygeldanamycin and rapamycin derivs., and phospholipase-directed signaling may be modulated by alkylphospholipids. Farnesyltransferase inhibitors were originally developed as inhibitors of ras-driven signals but may have activity by affecting other or addnl. targets. Signal transduction will remain a fertile basis for suggesting **cancer** treatments of the future, the evaluation of which should include monitoring effects of the drugs on their intended target signaling mols. in preclin. and early clin. studies.

L3 ANSWER 45 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:39629 Document No. 138:269401 ERBB2 Up-Regulates S100A4 and Several other Prometastatic Genes in Medulloblastoma. Hernan, Roberto; Fasheh, Rami; Calabrese, Christopher; Frank, Adrian J.; Maclean, Kirsteen H.; Allard, David; Barraclough, Roger; Gilbertson, Richard J. (Life Sciences Building, and School of Biological Sciences, Tennessee 38105, Memphis, St. Jude Children's Research Hospital, Departments of Developmental Neurobiology and Biochemistry, University of Liverpool, Liverpool, L69 7ZB, UK). Cancer Research, 63(1), 140-148 (English) 2003. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Medulloblastoma is frequently disseminated throughout the central nervous system by the time of diagnosis. Conventional therapeutic approaches have not reduced the high mortality associated with metastatic medulloblastoma and little is known regarding the mol. mechanisms that promote tumor invasion. Previously, we reported that overexpression of ERBB2 in medulloblastoma is associated with poor prognosis and metastasis. Here, we demonstrate that ERBB2 overexpression increases the migration of medulloblastoma cells across basement membranes in vitro. Furthermore, using microarray expression profiling, we show that ERBB2 up-regulates the expression of prometastatic genes in medulloblastoma cells. These include S100A4, which was previously shown to promote metastasis of breast **cancer**. We demonstrate that S100A4 is a direct target of ERBB2 signaling in medulloblastoma cells via a pathway involving phosphatidylinositol 3-kinase, AKT1, and extracellular signal-regulated kinase 1/2 and that levels of ERBB2 and S100A4 are tightly correlated in samples of primary medulloblastoma. Finally, we show that ERBB2-dependent medulloblastoma cell invasion in vitro and prometastatic gene expression in vivo can be blocked using the ERBB tyrosine kinase inhibitor OSI-774. These data identify an ERBB2 driven prometastatic pathway that may provide a novel target for therapeutic intervention in metastatic medulloblastoma.

L3 ANSWER 46 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2003:8967 Document No. 139:62338 Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents. Laird, A. Douglas; Cherrington, Julie M. (SUGEN, Inc., South San Francisco, CA, 94080, USA). Expert Opinion on Investigational Drugs, 12(1), 51-64 (English) 2003. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications Ltd..

AB A review. Numerous small mol. synthetic tyrosine kinase inhibitors are in clin. development for the treatment of human cancers. These fall into three broad categories: inhibitors of the epidermal growth factor receptor tyrosine kinase family (e.g., Iressa and Tarceva), inhibitors of the split kinase domain receptor tyrosine kinase subgroup (e.g., PTK787/ZK 222584 and SU11248) and inhibitors of tyrosine kinases from multiple subgroups (e.g., Gleevec). In addition, agents targeting other tyrosine kinases implicated in **cancer**, such as Met, Tie-2 and Src, are in preclin. development. As experience is gained in the clinic, it has become clear that unleashing the full therapeutic potential of tyrosine kinase inhibitors will require patient preselection, better assays to guide dose selection, knowledge of mechanism-based side effects and ways to predict and overcome drug resistance.

L3 ANSWER 47 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2002:974164 Document No. 139:143003 Clinical evaluation of agents targeting epidermal growth factor receptor (EGFR) in **cancer**. Lin, Edward H.; Abbruzzese, James L. (Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA). Oncogene-Directed Therapies, 313-330. Editor(s): Rak, Janusz. Humana Press Inc.: Totowa, N. J. ISBN: 0-89603-982-X (English) 2003. CODEN: 69DKTX.

AB A review. Proteins encoded by oncogenes and tumor-suppressor genes are the essential signaling components of the complex cellular signaling networks. **Cancer** arises from a multi-step process promoted by the imbalanced growth signals as a consequence of gain of oncogene and/or loss of tumor suppressor genes. The six essential **cancer** hallmarks include persistent cell growth signals, insensitivity to anti-growth signals, evasion of apoptosis, persistent angiogenesis, gain of cell immortality, and tumor invasion and metastasis. As an oncogene, gain of epidermal growth factor receptor (EGFR) function is achieved through EGFR over-expression and has been shown to be associated with almost all the six essential hallmarks of **cancer** except the gain of cell immortality. In various exptl. models, EGFR inhibition leads to regression of tumor cell growth, inhibition of angiogenesis, induction of apoptosis, and inhibition of tumor invasion and metastasis. Furthermore, over-expression of EGFR, frequently observed in a number of human cancers, is associated with poor overall prognosis, increased tumor recurrence, and decreased patient survival. The hypothesis that EGFR might be a **cancer** therapeutic target was proposed by Mendelsohn in the early 1980s; emerging only recently are the promising clin. trial results from a number of EGFR antagonists in different human cancers. This review will discuss the clin. developments and future directions of EGFR antagonists in **cancer** treatment.

L3 ANSWER 48 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:606437 Document No. 141:140461 Preparation of isopurines and related compounds as tyrosine kinase inhibitors for the treatment of **cancer**.. Beaulieu, Francis; Ouellet, Carl; Zimmermann, Kurt; Velaparthi, Upender; Wittman, Mark D. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2004063151 A2 20040729, 65 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2.
APPLICATION: WO 2004-US38 20040105. PRIORITY: US 2003-PV437926 20030103.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004063151	A2	20040729	WO 2004-US38	20040105

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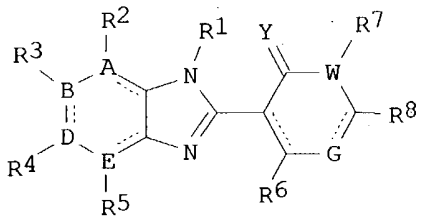
GI



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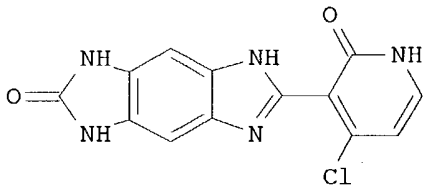

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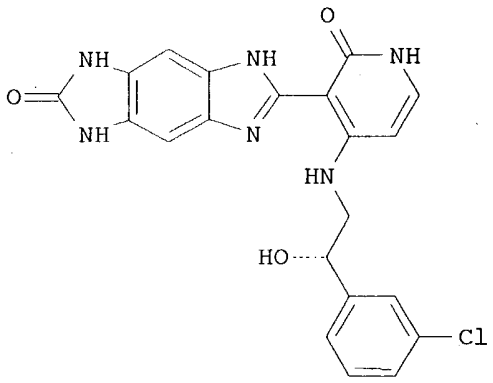

III

AB Title compds. I [A, B, D, E = C or N with provisos; X = N, C provided that if A, B, D, and E are each C, then at least one of R2 and R3, R3 and R4, or R4 and R5 is taken together to form a heterocyclic ring having at least one nitrogen atom; G = (X)n; X = N, C with provisos; n = 0-3; Y = O, S; W = N, C, O, etc.; R1, R2, R3, R4, R5, R6, R7, R8 = H, alkyl, alkenyl, etc.;] and their pharmaceutically acceptable salts were prepared For example, condensation of (S)-2-(3-chlorophenyl)-2-hydroxyethylamine and chloropyridone II, e.g., prepared from 4-iodo-2methoxypyridine-3-carbaldehyde in 2-steps, afforded benzoimidazole III. In tyrosine kinase inhibition assays, compds. I showed kinase activity of <25 μM against one or more of the following kinases CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF and VEGF. Compds. I are claimed useful as protein tyrosine kinase inhibitors, making them useful as anti-**cancer** agents.

L3 ANSWER 49 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:565076 Document No. 141:117130 Inhibition of melanogenesis and melanoma metastasis with p-aminobenzoic acid (PABA). Brooks, Peter C.; Morais, Danielle; Rodriguez, Dorothy (New York University, USA). PCT Int. Appl. WO 2004058241 A1 20040715, 53 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US41179 20031224. PRIORITY: US 2002-PV436394 20021224.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2004058241 A1 20040715 WO 2003-US41179 20031224
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004167222 A1 20040826 US 2003-746206 20031223

AB The present invention relates to the inhibition of melanogenesis with p-aminobenzoic acid (PABA) and its use in treating melanotic **cancer**. Combination treatment with carboplatin, paclitaxel, and PABA was effective against metastatic malignant melanoma in a patient whose melanoma both re-occurred following completed chemotherapy and progressed while she on chemotherapy.

L3 ANSWER 50 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:559502 Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors. Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-yu; James, Ray A.; Bishop, W. Robert; Wang, James J.-S.; Desai, Jagdish A. (Schering Corporation, USA). U.S. Pat. Appl. Publ. US 20040122018 A1 20040624, 731 pp., Cont.-in-part of U.S. Ser. No. 85,896. (English). CODEN: USXXCO. APPLICATION: US 2002-XB325896 20021219. PRIORITY: US 2001-940811 20010828; US 2002-85896 20020227; US 2002-325896 20021219.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004122018	A1	20040624	US 2002-325896	20021219
	US 2002198216	A1	20021226	US 2001-940811	20010828
	US 2003229099	A1	20031211	US 2002-85896	20020227
	US 2004122018	A1	20040624	US 2002-325896	20021219

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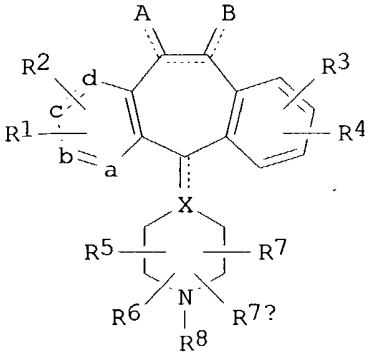

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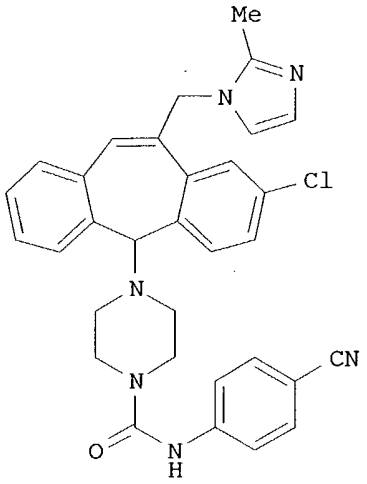

II

AB Title benzo[5,6]cyclohepta[1,2-b]pyridines and analogs (I) [wherein one of a, b, d, e = N, N=O; remaining a, b, d, e = C substituted with R1 or R2; or each a, b, d, e = C substituted with R1 or R2; X = N, C, CH; A, B = independently H, (un)substituted R9, carbamoyl(alkyl), amino(alkyl), acylamino(alkyl), ureido(alkyl), etc.; R1-R4 = independently H, halo, CF3, alkoxy, amino, NO2, CN, alkyl, alkenyl, alkynyl, etc.; R5-R7a = independently H, CF3, acyl, alkyl, aryl; R8 = H, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, etc.; R9 = (un)substituted heteroaryl(alkyl), arylalkoxy, heterocyclyl(alkyl), etc.; and stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs thereof] were prepared as farnesyl protein transferase (FPT) inhibitors. For example, a multi-step synthesis starting from tert-Bu 4-[8-chloro-6-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperazinecarboxylate, 2-methylimidazole, and p-cyanophenyl isocyanate gave (S)-II. The latter inhibited tumor growth of mouse H-Ras fibroblasts, HTB-177 human non-small cell lung **cancer** cells, and LOX human melanoma cells by 98% (60 MPK, p.o., BID, x2), 96% (80 MPK, p.o., BID, x3), and 90.3% (60 MPK, p.o., BID, x1), resp. Compds. of the invention inhibited FPT activity with IC50 values in the range of 0.05 nM to 100 nM and suppressed anchorage-independent growth of human tumor cells in a soft agar assay with IC50 values in the range of <0.5 nM to 50 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of proliferative diseases, such as **cancer**.

L3 ANSWER 51 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:559501 Document No. 141:106498 Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors. Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-yu; James, Ray A.; Bishop, W. Robert; Wang, James J.-S.; Desai, Jagdish A. (Schering Corporation, USA). U.S. Pat. Appl. Publ. US 2004122018 A1 20040624, 731 pp., Cont.-in-part of U.S. Ser. No. 85,896. (English). CODEN: USXXCO. APPLICATION: US 2002-XA325896 20021219. PRIORITY: US 2001-940811 20010828; US 2002-85896 20020227; US 2002-325896 20021219.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 2004122018	A1	20040624	US 2002-325896	20021219
	US 2002198216	A1	20021226	US 2001-940811	20010828
	US 2003229099	A1	20031211	US 2002-85896	20020227
	US 2004122018	A1	20040624	US 2002-325896	20021219

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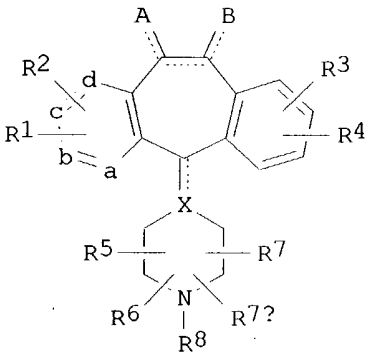

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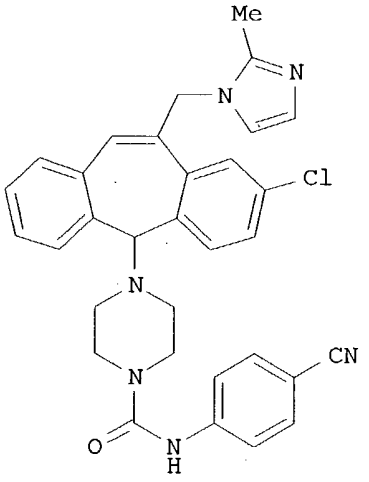

II

AB Title benzo[5,6]cyclohepta[1,2-b]pyridines and analogs (I) [wherein one of a, b, d, e = N, N=O; remaining a, b, d, e = C substituted with R1 or R2; or each a, b, d, e = C substituted with R1 or R2; X = N, C, CH; A, B = independently H, (un)substituted R9, carbamoyl(alkyl), amino(alkyl), acylamino(alkyl), ureido(alkyl), etc.; R1-R4 = independently H, halo, CF3, alkoxy, amino, NO2, CN, alkyl, alkenyl, alkynyl, etc.; R5-R7a = independently H, CF3, acyl, alkyl, aryl; R8 = H, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, etc.; R9 = (un)substituted heteroaryl(alkyl), arylalkoxy, heterocyclyl(alkyl), etc.; and stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs thereof] were prepared as farnesyl protein transferase (FPT) inhibitors. For example, a multi-step synthesis starting from tert-Bu 4-[8-chloro-6-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperazinecarboxylate, 2-methylimidazole, and p-cyanophenyl isocyanate gave (S)-II. The latter inhibited tumor growth of mouse H-Ras fibroblasts, HTB-177 human non-small cell lung **cancer** cells, and LOX human melanoma cells by 98% (60 MPK, p.o., BID, x2), 96% (80 MPK, p.o., BID, x3), and 90.3% (60 MPK, p.o., BID, x1), resp. Compds. of the invention inhibited FPT activity with IC50 values in the range of 0.05 nM to 100 nM and suppressed anchorage-independent growth of human tumor cells in a soft agar assay with IC50 values in the range of <0.5 nM to 50 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of proliferative diseases, such as **cancer**.

L3 ANSWER 52 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:533970 Document No. 141:65088 Methods and compositions for the prevention or treatment of neoplasia comprising a COX-2 inhibitor in combination with an epidermal growth factor receptor antagonist.

Masferrer, Jaime (Pharmacia Corporation, USA). U.S. Pat. Appl. Publ. US 2004127470 A1 20040701, 103 pp., Cont.-in-part of U.S. Ser. No. 470,951. (English). CODEN: USXXCO. APPLICATION: US 2003-651916 20030829. PRIORITY: US 1998-PV113786 19981223; US 1999-470951 19991222.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004127470	A1	20040701	US 2003-651916	20030829

AB The present invention relates to a novel method of preventing and/or treating neoplasia disorders in a subject that is in need of such prevention or treatment by administering to the subject at least one COX-2 inhibitor in combination with an EGF receptor antagonist. Compns., pharmaceutical compns. and kits are also described.

L3 ANSWER 53 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:513328 Document No. 141:71561 Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors. Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-yu; James, Ray A.; Bishop, W. Robert; Wang, James J.-S.; Desai, Jagdish A. (Schering Corporation, USA). U.S. Pat. Appl. Publ. US 2004122018 A1 20040624, 731 pp., Cont.-in-part of U.S. Ser. No. 85,896. (English). CODEN: USXXCO. APPLICATION: US 2002-325896 20021219. PRIORITY: US 2001-940811 20010828; US 2002-85896 20020227.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004122018	A1	20040624	US 2002-325896	20021219
	US 2002198216	A1	20021226	US 2001-940811	20010828
	US 2003229099	A1	20031211	US 2002-85896	20020227
	US 2004122018	A1	20040624	US 2002-325896	20021219
	US 2004122018	A1	20040624	US 2002-325896	20021219
	WO 2003072549	A1	20030904	WO 2003-US5479	20030225

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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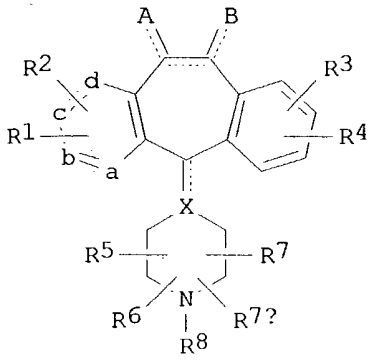

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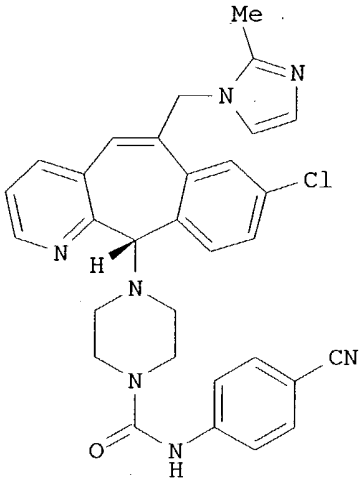

II

AB Title benzo[5,6]cyclohepta[1,2-b]pyridines and analogs (I) [wherein one of a, b, d, e = N, N=O; remaining a, b, d, e = C substituted with R1 or R2; or each a, b, d, e = C substituted with R1 or R2; X = N, C, CH; A, B = independently H, (un)substituted R9, carbamoyl(alkyl), amino(alkyl), acylamino(alkyl), ureido(alkyl), etc.; R1-R4 = independently H, halo, CF3, alkoxy, amino, NO2, CN, alkyl, alkenyl, alkynyl, etc.; R5-R7a = independently H, CF3, acyl, alkyl, aryl; R8 = H, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, etc.; R9 = (un)substituted heteroaryl(alkyl), arylalkoxy, heterocyclyl(alkyl), etc.; and stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs thereof] were prepared as farnesyl protein transferase (FPT) inhibitors. For example, a multi-step synthesis starting from tert-Bu 4-[8-chloro-6-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperazinecarboxylate, 2-methylimidazole, and p-cyanophenyl isocyanate gave (S)-II. The latter inhibited tumor growth of mouse H-Ras fibroblasts, HTB-177 human non-small cell lung **cancer** cells, and LOX human melanoma cells by 98% (60 MPK, p.o., BID, x2), 96% (80 MPK, p.o., BID, x3), and 90.3% (60 MPK, p.o., BID, x1), resp. Compds. of the invention inhibited FPT activity with IC50 values in the range of 0.05 nM to 100 nM and suppressed anchorage-independent growth of human tumor cells in a soft agar assay with IC50 values in the range of <0.5 nM to 50 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of proliferative diseases, such as **cancer**.

L3 ANSWER 54 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:453016 Document No. 141:1227 Combination **cancer** therapy with a glutathione S-transferase (GST)-activated anticancer compound and another anticancer therapy. Xu, Hua; Brown, Gail L.; Schow, Steven R.; Keck, James G. (Telik, Inc., USA). PCT Int. Appl. WO 2004045593 A2 20040603, 38 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, EG, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.

(English). CODEN: PIXXD2. APPLICATION: WO 2003-US36209 20031114.
PRIORITY: US 2002-PV426983 20021115.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004045593	A2	20040603	WO 2003-US36209	20031114
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	US 2004138140	A1	20040715	US 2003-714593	20031114

AB The invention discloses a method for combination **cancer** therapy in a mammal, especially a human, by administering a therapeutically effective amount of a GST-activated anticancer compound and a therapeutically ED of another anticancer therapy. Also disclosed are pharmaceutical compns., products, and kits for the method, as well as the use of a GST-activated anticancer compound in the manufacture of a medicament for the method. The invention further discloses a method for potentiating an anticancer therapy in a mammal, especially a human, comprising administering a therapeutically effective amount of a GST-activated anticancer compound to the mammal being treated with the anticancer therapy. Further disclosed is the use of a GST-activated anticancer compound in the manufacture of a medicament for the method. The GST-activated anticancer compound is preferably a compound of US Patent Number 5,556,942, and more preferably TLK286, especially as the hydrochloride salt.

L3 ANSWER 55 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:432009 Document No. 141:684 Antitumor activity of erlotinib (OSI-774, Tarceva) alone or in combination in human non-small cell lung **cancer** tumor xenograft models. Higgins, Brian; Kolinsky, Kenneth; Smith, Melissa; Beck, Gordon; Rashed, Mohammad; Adames, Violeta; Linn, Michael; Wheeldon, Eric; Gand, Laurent; Birnboeck, Herbert; Hoffmann, Gerhard (Department of Oncology, In Vivo Section, Hoffmann-La Roche Inc, Nutley, NJ, USA). Anti-Cancer Drugs, 15(5), 503-512 (English) 2004. CODEN: ANTDEV. ISSN: 0959-4973. Publisher: Lippincott Williams & Wilkins.

AB Our objective was the preclin. assessment of the pharmacokinetics, monotherapy, and combined antitumor activity of the epidermal growth factor receptor (HER1/EGFR) Tyr kinase inhibitor erlotinib in athymic nude mice bearing non-small cell lung **cancer** (NSCLC) xenograft models. Immunohistochem. determined the HER1/EGFR status of the NSCLC tumor models. Pharmacokinetic studies assessed blood plasma drug concns. of erlotinib in tumor- and non-tumor-bearing athymic nude mice. These were followed by maximum tolerated dose (MTD) studies for erlotinib and each chemotherapy. Erlotinib was then assessed alone and in combination with these chemotherapies in the NSCLC xenograft models. Complete necropsies were performed on most of the animals in each study to further assess antitumor or toxic effects. Erlotinib monotherapy dose-dependently inhibited tumor growth in the H460a tumor model, correlating with circulating levels of drug. There was antitumor activity at the MTD with

each agent tested in both the H460a and A549 tumor models (erlotinib 100 mg/kg: 71 and 93% tumor growth inhibition; gemcitabine 120 mg/kg: 93 and 75% tumor growth inhibition; cisplatin 6 mg/kg: 81 and 88% tumor growth inhibition). When each compound was given at a fraction of the MTD, tumor growth inhibition was suboptimal. Combinations of gemcitabine or cisplatin with erlotinib were assessed at 25% of the MTD to determine efficacy. In both NSCLC models, doses of gemcitabine (30 mg/kg) or cisplatin (1.5 mg/kg) with erlotinib (25 mg/kg) at 25% of the MTD were well tolerated. For the slow growing A549 tumor, there was significant tumor growth inhibition in the gemcitabine/erlotinib and cisplatin/erlotinib combinations (above 100 and 98%, resp.), with partial regressions. For the faster growing H460a tumor, there was significant but less remarkable tumor growth inhibition in these same combinations (86 and 53% resp.). These results show that in NSCLC xenograft tumors with similar levels of EGFR expression, the antitumor activity of erlotinib is robust both as monotherapy and in combination with chemotherapies.

L3 ANSWER 56 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:430979 Document No. 141:5495 Altered patterns of protein phosphorylation associated with glioblastoma progression and their diagnostic detection with phospho-specific antibodies. Mischel, Paul S.; Sawyers, Charles L.; Smith, Bradley L.; Crosby, Katherine (The Regents of the University of California, USA; Cell Signaling Technology, Inc.). PCT Int. Appl. WO 2004044218 A2 20040527, 90 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US35115 20031105. PRIORITY: US 2002-PV423777 20021105.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004044218	A2	20040527	WO 2003-US35115	20031105
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	US 2004106141	A1	20040603	US 2003-701490	20031105

AB Proteins showing altered patterns of phosphorylation are identified for use in the diagnosis of gliomas, including glioblastoma multiforme. The proteins showing altered patterns of phosphoryaltion may also be targets for chemotherapy.

L3 ANSWER 57 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:387834 Document No. 140:368007 Rationale and clinical validation of epidermal growth factor receptor as a target in the treatment of head and neck **cancer**. Caponigro, Francesco (Instituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale", Naples, Italy).

Anti-Cancer Drugs, 15(4), 311-320 (English) 2004. CODEN: ANTDEV. ISSN: 0959-4973. Publisher: Lippincott Williams & Wilkins.

AB A review. Recurrent/metastatic head and neck **cancer** is an area of high, unmet treatment need. There is a strong rationale for targeting the epidermal growth factor receptor (EGFR) in head and neck **cancer** as most of these tumors express high levels of EGFR relative to normal tissue, with high expression correlating with poor patient outcome. This rationale has been validated in extensive preclin. studies. Two small mols. with EGFR inhibitory activity, gefitinib ("Iressa", ZD1839) and erlotinib ("Tarceva", OSI-774), and a humanized monoclonal antibody against the EGFR extracellular domain, cetuximab ("Erbitux", C225), are in clin. trials for advanced head and neck **cancer**. The initial results of these trials are promising. Gefitinib and erlotinib show activity as monotherapy in patients with recurrent or metastatic head and neck **cancer**, and have an acceptable safety profile compared with conventional chemotherapy. Gefitinib, which can be given at doses below the maximum tolerated dose, is associated with slightly lower rates of adverse events than erlotinib, which is dosed at the maximum tolerated dose. Combinations of cetuximab with radiotherapy or platinum-based chemotherapy have also shown activity in phase I/II studies. Both gefitinib and cetuximab have entered phase III studies. The results of these trials, which will mature over the next few years, will help determine the optimal use of EGFR agents in head and neck cancers.

L3 ANSWER 58 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:354796 Document No. 140:368653 Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of **cancer**. Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William (Astrazeneca AB, Swed.; Astrazeneca UK Limited). PCT Int. Appl. WO 2004035057 A1 20040429, 24 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB4347 20031007. PRIORITY: GB 2002-23854 20021012.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004035057	A1	20040429	WO 2003-GB4347	20031007

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable

salt thereof, is described. The combination of the invention is useful for the treatment of **cancer**, e.g. prostate **cancer**.

L3 ANSWER 59 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:310953 Document No. 140:321363 Preparation of [(piperazinyl)benzimidazolyl]quinolinones and analogs as tyrosine kinase inhibitors for treatment of **cancer**. Velaparthi, Upender; Wittman, Mark D. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2004030620 A2 20040415, 62 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US30669 20030929. PRIORITY: US 2002-PV415066 20020930.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004030620	A2	20040415	WO 2003-US30669	20030929
	WO 2004030620	A3	20040610		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004092514	A1	20040513	US 2003-674098	20030929

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I and II [wherein A, B, D, and E = independently C, N, O, S or a direct bond, provided that not more than one of A, B, D, and E can be a single bond; Y = O or S; W = N, CH, O, and S, provided that when W = O or S, R7 is absent; R1-R7 = independently H, alkyl, alkenyl, alkynyl, (hetero)cycloalkyl, halo, amino(alkyl), (thio)alkoxy, NO2, (hetero)aryl, (thio)alkoxyalkyl, aminoalkyl, (hetero)aralkyl, heterocycloalkylalkyl, CN, CO2R8, CONR9R10, CO2NR11R12, NR13CONR14R15, NR16SO2R17, SO2NR18R19, C(NR20)NR21R22, NHZ, or NHZ-(hetero)aryl; Z = (un)substituted (cyclo)alkyl, (cyclo)alkenyl, or alkynyl, optionally interrupted by CO, CONH, CNOR26, CNNR27, CNNCOR28, or CNNSO2R29; R8-R24 and R26 = independently H, alkyl, alkenyl, alkynyl, cycloalkyl(alkyl), OH, alkoxy, (hetero)aryl, heterocyclyl, heteroarylalkyl, alkyl-R25; R25 = alkenyl, OH, SH, (thio)alkoxy, NH2, (di)alkylamino, (hetero)aryl, CN, halo, heterocyclyl, sulfoxy, sulfonyl, NR27CO2R28, NR29COR30, NR31SO2R32, SO2NR31R32, or CONR33R34; R27-R34 = independently H, or (cyclo)alkyl; and enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs, or solvates thereof] were prepared as tyrosine kinase inhibitors.

For example, 1-[4-(3,4-diamino-5-methylphenyl)piperazin-1-yl]ethanone was condensed with 2,4-dichloroquinoline-3-carboxaldehyde in MeOH to give the benzimidazole. Hydrolysis of the chloro group using 4N HCl in dioxane afforded the 2- and 4-quinolinones. Nucleophilic addition of (S)-2-(3-chlorophenyl)-2-hydroxyethylamine using N-methylmorpholine in DMF provided III and IV. Compds. of the invention exhibited kinase activity of <25 μM against one or more of the following kinases: CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. Thus, I, II, and their pharmaceutical compns. are useful as for treatment of **cancer** and other diseases that can be treated by inhibiting tyrosine kinase enzymes (no data).

L3 ANSWER 60 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:308364 Document No. 140:321386 Preparation of vasculostatic agents and methods of use. Wrasidlo, Wolfgang; Doukas, John; Royston, Ivor; Noronha, Glenn; Hood, John D.; Dneprovskaia, Elena; Gong, Xianchang; Splittgerber, Ute; Zhao, Ningning (Targegen, Inc., USA). PCT Int. Appl. WO 2004030635 A2 20040415, 230 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US31721 20031003. PRIORITY: US 2002-PV415981 20021003; US 2003-PV440234 20030114; US 2003-PV443752 20030129; US 2003-PV463818 20030417; US 2003-PV466983 20030430; US 2003-PV479295 20030617.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004030635	A2	20040415	WO 2003-US31721	20031003
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004167198	A1	20040826	US 2003-679209	20031002

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. (2 Markush structures shown as I and II; others are described in the claims and disclosure; variables defined below; e.g. III and IV) and methods are provided for treating disorders associated with compromised vasculostasis. Invention methods and compns. are useful for treating a variety of disorders including for example, stroke, myocardial infarction, **cancer**, ischemia/reperfusion injury, autoimmune diseases such as rheumatoid arthritis, eye diseases such as retinopathies or macular

degeneration or other vitreoretinal diseases, inflammatory diseases, vascular leakage syndrome, edema, transplant rejection, adult/acute respiratory distress syndrome (ARDS), and the like. Although the methods of preparation are not claimed, many example prepns. are included. For example, III was prepared (75 %) from 2-(2-aminophenyl)indole and 4-hydroxyphenylacetic acid. Various expts. are described that show the use of the claimed compds. along with chemotherapeutic agents for **cancer** treatment. The claimed compds. also show inhibition of vascular leak induced by interleukin 2. Inhibition of VEGF-induced edema, reduction of myocardial infarction and inhibition of c-Src and Yes kinases were demonstrated for some of the claimed compds. For I: each R0 = -H, -COOH, -OR', -SO3H, wherein R' is - H or lower alkyl, or when x = 2, each R0 is taken together to form a 1,3-dioxolyl ring, or each R0 = (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, (un)substituted cycloalkyl, (un)substituted heterocyclic, (un)substituted aryl, (un)substituted heteroaryl, (un)substituted alkylaryl, (un)substituted arylalkyl, (un)substituted arylalkenyl, (un)substituted arylalkynyl, halogen, amino, amido, nitro, or thioalkyl. R1 and R2 = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, (un)substituted cycloalkyl, (un)substituted heterocyclic, (un)substituted aryl, (un)substituted heteroaryl, (un)substituted alkylaryl, (un)substituted arylalkyl, (un)substituted arylalkenyl, (un)substituted arylalkynyl; G is NH, O, S, or (CR'')p, wherein R'' is -H, lower alkyl, or acetamido, and wherein p = 0-3; Ar is aryl or heteroaryl, and x and y = 1-4. For II: Z1-Z6 = C, -C:O, N, or NRa, wherein Ra is -H, (un)substituted alkyl, wherein said substituents are halogen, hydroxy, oxo, or amino; each X = halogen, -ORb, -NRb2, or -SRb, wherein Rb is -H lower alkyl, -(CH2)2NHEt, -(CH2)3morpholin-1-yl, -(CH2)3-(N-methylpiperazin-1-yl), aryl, heteroaryl, -(NH-NH-Rc), -(N:N-NH-Rc), wherein Rc is H or lower alkyl. Each Y = -ORd, -NRd2, -SRd, or -OPO3H2 wherein Rd is H, lower alkyl, aryl, heteroaryl, -(CH2)2NHEt, -(CH2)3morpholin-1-yl, or (CH2)3-(N-methylpiperazin-1-yl); or each Y = (un)substituted alkyl, (un)substituted aryl, (un)substituted heteroaryl, or halogen, wherein said substituents = halogen, -ORe, -NRe2, -SRe, -P(O)(OH)2, wherein Re is -H, lower alkyl, aryl, or heteroaryl; or each Y = CH2glycinyl, CH2NHëthoxy, CH2NHCH2alkyl, CH2NHCH2t-Bu, CH2NHCH2aryl, CH2NHCH2substituted aryl, CH2NHCH2heteroaryl, CH2NHCH2substituted heteroaryl; or when n is 2, each Y is taken together to form a fused aromatic or heteroarom. ring system; and m and n = 1 to 4, wherein when Z1, Z3, Z5, and Z6 are each N, X is NH2, and m = n = 2, Y is not Ph or 4-hydroxyphenyl.

L3 ANSWER 61 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:220336 Document No. 140:270873 Preparation of pyrazolopyrimidines as cyclin-dependent kinase inhibitors. Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Mallams, Alan; Alvarez, Carmen S.; Keertikar, Kartik M.; Rivera, Jocelyn; Chan, Tin-yau; Madison, Vincent; Fischmann, Thierry O.; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon; Paradkar, Vidyadhar M.; Hobbs, Douglas Walsh (Schering Corporation, USA; Pharmacopeia, Inc.). PCT Int. Appl. WO 2004022561 A1 20040318, 609 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD,

TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US27555 20030903. PRIORITY: US 2002-PV408027 20020904; US 2002-PV421959 20021029.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004022561	A1	20040318	WO 2003-US27555	20030903

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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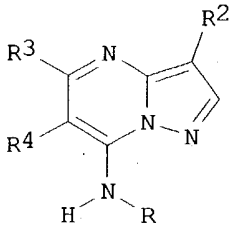

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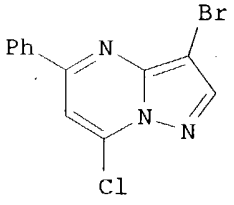

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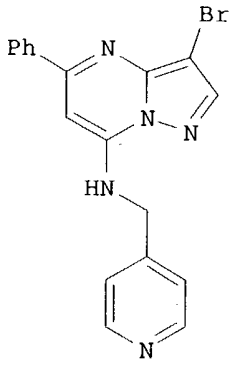

III

AB The title compds. [I R = H, alkyl, cycloalkyl, etc.; R2 = alkyl, halo, aryl, etc.; R3 = H, halo, aryl, etc.; R4 = H, halo, alkyl], useful as inhibitors of cyclin dependent kinases for treatment, prevention, inhibition, or amelioration of one or more diseases associated with the CDKs such as **cancer**, were prepared Thus, reacting II (preparation given) with 4-aminomethylpyridine afforded 93% III which showed IC50 of 0.020 μM and 0.029 μM against CDK2 kinase (cyclin A or cyclin E-dependent). The pharmaceutical composition comprising the compound I is claimed. This is a Part I of I-III series.

L3 ANSWER 62 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:220335 Document No. 140:270872 Preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents.

Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon (Schering Corporation, USA; Pharmacopeia, Inc.). PCT Int. Appl. WO 2004022560 A1 20040318, 82 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US27502 20030903. PRIORITY: US 2002-PV407999 20020904.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004022560	A1	20040318	WO 2003-US27502	20030903
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004116442	A1	20040617	US 2003-653868	20030903

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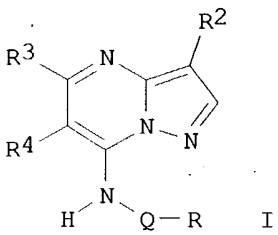

I

AB The title compds. [I; Q = SO2, CO; R = each (un)substituted aryl or heteroaryl; R2 = cyano, NR5R6, CO2R6, CONR5R6, OR6, SR6, SO2R7, SO2NR5R6, -N(R5)SO2R7, N(R5)COR7, N(R5)CONR5R6, alkynyl, heteroaryl, CF3, heterocyclyl, alkynylalkyl, cycloalkyl, (un)substituted alkyl; R3 = H, halogen, NR5R6, CONR5R6, each (un)substituted alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, etc.; R4 = H, halo, alkyl; R5 = H, alkyl; R6 = H, each (un)substituted alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; or R5 and R6 in the moiety -NR5R6, may be joined together to form an (un)substituted cycloalkyl or heterocyclyl] or pharmaceutically acceptable salts or solvates thereof are prepared In its many embodiments, the present invention also provides methods of preparing such compds., pharmaceutical compns. containing one or more such compds. I, methods of preparing pharmaceutical formulations comprising one or more such compds., and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with cyclin dependent kinase using such compds. I or

pharmaceutical compns. The disease associated with cyclin dependent kinase is selected from the group consisting of; (1) **cancer** of the bladder, breast, colon, kidney, liver, lung, small cell lung **cancer**, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (2) leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; (3) acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia; (4) fibrosarcoma and rhabdomyosarcoma; (5) astrocytoma, neuroblastoma, glioma and schwannomas; and (6) melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular **cancer** and Kaposi's sarcoma.

L3 ANSWER 63 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:220334 Document No. 140:270871 Preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents. Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon (Schering Corporation, USA; Pharmacopeia, Inc.). PCT Int. Appl. WO 2004022559 A1 20040318, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US27405 20030903. PRIORITY: US 2002-PV408030 20020904.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004022559	A1	20040318	WO 2003-US27405	20030903
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004102451	A1	20040527	US 2003-654157	20030903

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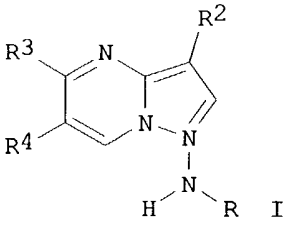

I

AB The title compds. [I; R = (un)substituted heteroaryl; R2 = (un)substituted alkyl, alkynyl, aryl, heteroaryl, alkynylalkyl, CF3, heterocyclylalkyl, alkynylalkyl, cycloalkyl, CO2R4, etc., wherein aryl is optionally substituted; R3 = H, halogen, NR5R6, CO2R4, CONR5R6, each (un)substituted alkyl, alkynyl, cycloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, or heteroaryl, etc.; R4 = H, halo, alkyl; R5 = H, alkyl; R6 = H, each (un)substituted alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; or R5 and R6 in the moiety -NR5R6, may be joined together to form an (un)substituted cycloalkyl or heterocyclyl] or pharmaceutically acceptable salts or solvates thereof are prepared In its many embodiments, the present invention also provides methods of preparing such compds., pharmaceutical compns. containing one or more such compds. I, methods of preparing pharmaceutical formulations comprising one or more such compds., and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with cyclin dependent kinase using such compds. I or pharmaceutical compns. The disease associated with cyclin dependent kinase is selected from the group consisting of; (1) **cancer** of the bladder, breast, colon, kidney, liver, lung, small cell lung **cancer**, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (2) leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; (3) acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia; (4) fibrosarcoma and rhabdomyosarcoma; (5) astrocytoma, neuroblastoma, glioma and schwannomas; and (6) melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular **cancer** and Kaposi's sarcoma.

L3 ANSWER 64 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:220207 Document No. 140:270868 Preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents. Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Knutson, Chad; Mckittrick, Brian; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon (Schering Corporation, USA; Pharmacopeia, Inc.). PCT Int. Appl. WO 2004022062 A1 20040318, 77 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US27564 20030903. PRIORITY: US 2002-PV408182 20020904.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004022062	A1	20040318	WO 2003-US27564	20030903

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,

NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004102452 A1 20040527 US 2003-654163 20030903

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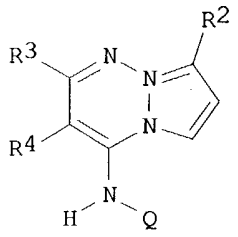

I

AB The title compds. [I; Q = SO2NR6R7, CONR6R7, CO2R7; R2 = (un)substituted alkyl, alkynyl, alkynylalkyl, cycloalkyl, CF3, CO2R6, aryl, arylalkyl, heteroarylalkyl, heterocyclyl, etc., wherein aryl is optionally substituted; R3 = H, halogen, NR5R6, CONR5R6, CO2R4, each (un)substituted alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, etc.; R4 = H, halo, alkyl; R5 = H, alkyl; R6 = H, each (un)substituted alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; R7 = each (un)substituted alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; or R5 and R6 in the moiety -NR5R6, may be joined together to form an (un)substituted cycloalkyl or heterocyclyl] or pharmaceutically acceptable salts or solvates thereof are prepared In its many embodiments, the present invention also provides methods of preparing such compds., pharmaceutical compns. containing one or more such compds. I, methods of preparing pharmaceutical formulations comprising one or more such compds., and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with cyclin dependent kinase using such compds. I or pharmaceutical compns. The disease associated with cyclin dependent kinase is selected from the group consisting of; (1) **cancer** of the bladder, breast, colon, kidney, liver, lung, small cell lung **cancer**, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (2) leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; (3) acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia; (4) fibrosarcoma and rhabdomyosarcoma; (5) astrocytoma, neuroblastoma, glioma and schwannomas; and (6) melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular **cancer** and Kaposi's sarcoma.

L3 ANSWER 65 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:182584 Document No. 140:235710 Preparation of 2-(4-substituted-2-oxo-1,2-dihydropyridin-3-yl)-benzimidazoles as novel tyrosine kinase inhibitors. Wittman, Mark D.; Balasubramanian, Neelakantan; Velaparthi, Upender; Zimmermann, Kurt; Saulnier, Mark G.; Liu, Peiying; Sang, Xiaopeng; Frennesson, David B.; Stoffan, Karen M.; Tarrant, James G.; Marinier, Anne; Roy, Stephan (USA). U.S. Pat. Appl. Publ. US 2004044203 A1 20040304, 210 pp., Cont.-in-part of U.S. Ser. No. 105,599. (English).

CODEN: USXXCO. APPLICATION: US 2002-263448 20021002. PRIORITY: US 2001-PV279327 20010328; US 2002-105599 20020325.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004044203	A1	20040304	US 2002-263448	20021002
	WO 2004031401	A2	20040415	WO 2003-US30931	20031001
	WO 2004031401	A3	20040729		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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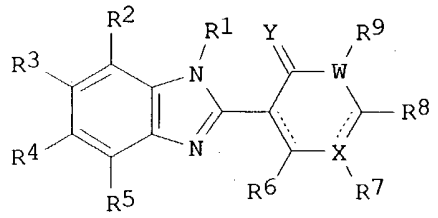

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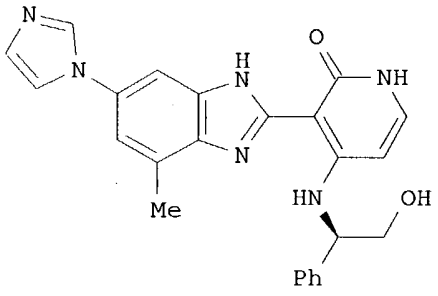

II

AB The title compds. [I; X = N, C, a bond, etc.; Y = O, S; W = N, C, O, S (if W = O or S, then R9 is absent); R1-R9 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts which inhibit tyrosine kinase enzymes thereby making them useful as anti-**cancer** agents, were prepared Thus, reacting 3-[6-(imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-iodo-1H-pyridin-2-one (preparation given) with (S)-(-)-2-phenylglycinol in the presence of N-methylmorpholine in DMF afforded 52% (S)-II. The compds. I showed kinase activity of <25μM against one or more of the following kinases CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. The compds. I are also useful for the treatment of other diseases which can be treated by inhibiting tyrosine kinase enzymes.

L3 ANSWER 66 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:120750 Document No. 140:175121 Therapeutic inhibition of protein kinases and a cellular ATP synthetic pathway in **cancer** cells. Carson, Dennis A.; Rosenbach, Michael D.; Carrera, Carlos J.; Leoni, Lorenzo M. (The Regents of the University of California, USA; Salmedix, Inc.). PCT Int. Appl. WO 2004012769 A1 20040212, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US24439 20030801. PRIORITY: US 2002-PV400568 20020802.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004012769	A1	20040212	WO 2003-US24439	20030801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004096436	A1	20040520	US 2003-632592	20030801

AB The present invention provides methods of treating **cancer** using inhibitors of protein kinases. The inhibitors of protein kinases are combined with agents that inhibit a cellular ATP synthetic pathway. Inhibitors of ATP synthesis include inhibitors of de novo purine biosynthesis, inhibitors of the salvage pathway of ATP biosynthesis, and inhibitors of the enzyme inosine monophosphate dehydrogenase.

L3 ANSWER 67 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:108293 Document No. 140:354496 The HER receptor family: a rich target for therapeutic development. Mass, Robert D. (Genentech BioOncology, Inc., South San Francisco, CA, 94080-4990, USA). International Journal of Radiation Oncology, Biology, Physics, 58(3), 932-940 (English) 2004. CODEN: IOBPD3. ISSN: 0360-3016. Publisher: Elsevier Science Inc..

AB A review. The key role of the HER family of receptors in **cancer** was widely acknowledged. HER receptor activation occurs via ligand binding or nonligand-dependent receptor dimerization, initiating signals that promote tumorigenesis via cell proliferation, survival, migration, adhesion, and differentiation. Therapeutic strategies designed to target and inhibit HER activation that are in clin. development are reviewed, including examples of both small-mol. tyrosine kinase inhibitors and monoclonal antibodies. Tarceva is a potent, highly selective, reversible inhibitor of HER1/epidermal growth factor receptor tyrosine kinase with inhibitory activity against various in vitro and in vivo models of solid human tumors. Phase II trials in refractory non-small-cell lung, head-and-neck, and ovarian **cancer** have demonstrated clin. activity, including objective responses and prolonged, stable disease. Four Phase III trials are ongoing evaluating primarily the effect on

survival of Tarceva in combination with chemotherapy. 2C4 is a humanized anti-HER2 monoclonal antibody that binds to a broad, extracellular epitope, resulting in steric inhibition of HER-receptor complex formation that involves HER2. 2C4 has shown significant activity in xenograft models of prostate, lung, and breast **cancer**. 2C4's activity, unlike Herceptin's, is not dependent on HER2 amplification. This antibody is in early clin. development. The strategy of targeting the HER system was further validated by early experience with Tarceva and 2C4. The optimal clin. benefit of these agents will likely involve combinations of biol. agents, with or without traditional chemotherapy, and will be guided by critical predictive diagnostic information.

L3 ANSWER 68 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:100947 Document No. 140:139486 Method of treating **cancer**. Potter, David A. (Advanced Research & Technology Institute at Indiana University, USA). PCT Int. Appl. WO 2004010937 A2 20040205, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US23437 20030728. PRIORITY: US 2002-PV399573 20020726.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004010937	A2	20040205	WO 2003-US23437	20030728
	WO 2004010937	A3	20040527		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004167139	A1	20040826	US 2003-629045	20030728

AB Methods for treating **cancer** are described here. The methods include administering to an HIV-neg. patient an m-calpain inhibitor such as ritonavir. Ritonavir or other m-calpain inhibitors can also be co-administered with other therapeutic agents such as a Cox-2 inhibitor, a taxane, or a proteasome inhibitor. Methods for determining whether a patient will respond to a particular method of treatment are also described herein.

L3 ANSWER 69 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN
2004:41229 Document No. 140:105266 Boroproline compound combination therapy for various diseases. Adams, Sharlene; Miller, Glenn T.; Jesson, Michael I.; Jones, Barry (Point Therapeutics, Inc., USA). PCT Int. Appl. WO 2004004661 A2 20040115, 125 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,

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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004004661	A2	20040115	WO 2003-US21547	20030709
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
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	US 2004077601	A1	20040422	US 2003-616694	20030709

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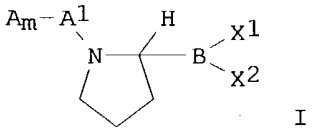

I

AB A method is provided for treating subjects with combination therapy including compds. of Formula I (wherein m is an integer between 0 and 10, inclusive; A and A1 may be L- or D-amino acid residues, the C bonded to B is in the L-configuration, and each X1 and X2 is, independently, a hydroxy group or a group capable of being hydrolyzed to a hydroxy group in aqueous solution at physiol. pH). It was surprisingly discovered that this combination enhanced the efficacy of both agents, and that administration of Formula I compds. induced cytokine and chemokine production in vivo. The combinations can be used to enhanced ADCC, stimulate immune responses and /or patient and treat certain disorders. The invention also relates to kits and compns. relating to such combinations.

L3 ANSWER 70 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:41226 Document No. 140:105321 Methods and compositions relating to isoleucine boroproline compounds. Adams, Sharlene; Miller, Glenn T.; Jesson, Michael I.; Jones, Barry (Point Therapeutics, Inc., USA). PCT Int. Appl. WO 2004004658 A2 20040115, 152 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO

2003-US21405 20030709. PRIORITY: US 2002-PV394856 20020709; US 2002-PV414978 20021001; US 2003-PV466435 20030428.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004004658	A2	20040115	WO 2003-US21405	20030709
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004077601	A1	20040422	US 2003-616694	20030709

AB A method for treating subjects with, inter alia, abnormal cell proliferation or infectious disease using agents of formula (I, AmNHCH(CH(CH3)CH2CH3)COA1R) (where Am and A1 are amino acids and R = organo boronates, organo phosphonates, fluoroalkyl ketones, alphaketos, N-peptiolyl-O-(acylhydroxylamines), azapeptides, azetidines, fluoroolefins dipeptide isosteres, peptidyl (α-aminoalkyl) phosphonate esters, aminoacyl pyrrolidine-2-nitriles and 4-cyanothiazolidides) is claimed. Methods for stimulating an immune response using the compds. of the invention are also claimed. Compns. containing Ile-boroPro compds. are also provided as are kits containing the compns. The invention embraces the use of these compds. alone or in combination with other therapeutic agents.

L3 ANSWER 71 OF 71 CAPLUS COPYRIGHT 2004 ACS on STN

2004:41213 Document No. 140:105249 Combination of mTOR inhibitor and a tyrosine kinase inhibitor for the treatment of neoplasms. Neel, Benjamin G.; Mohi, Golam (Beth Israel Deaconess Medical Center, USA). PCT Int. Appl. WO 2004004644 A2 20040115, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US20972 20030703. PRIORITY: US 2002-PV394029 20020705; US 2002-PV412402 20020920.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004004644	A2	20040115	WO 2003-US20972	20030703
	WO 2004004644	A3	20040506		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,				

GW, ML, MR, NE, SN, TD, TG

AB The invention features methods and compns. including an mTOR inhibitor and a tyrosine kinase inhibitor for reducing the proliferation of and enhancing the apoptosis of neoplastic cells. The addition of an MEK inhibitor to this combination further enhances the effectiveness of this therapeutic method.

L8 32 SORT L5 PY

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L8 ANSWER 1 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2002:74864 Document No. 137:134227 Epidermal growth factor receptor tyrosine kinase inhibitors in **cancer** therapy. Adjei, Alex A. (Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA). Drugs of the Future, 26(11), 1087-1092 (English) 2001. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.

AB A review. Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will summarize current preclin. and clin. knowledge of the small-mol. oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.

L8 ANSWER 2 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2001:921398 Document No. 137:87979 Anticancer therapy targeting the ErbB family of receptor tyrosine kinases. Slichenmyer, William J.; Fry, David W. (Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA). Seminars in Oncology, 28(5, Suppl. 16), 67-79 (English) 2001. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..

AB Several agents that target one or more members of the erbB family of receptor tyrosine kinases are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast **cancer** when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities associated with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development. The orally active tyrosine kinase inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI774, and CI-1033. Evidence to data suggests that the major role for erbB receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

L8 ANSWER 3 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2001:839156 Document No. 136:144494 Lung **cancer**. Evans, Tracey

L.; Lynch, Thomas J., Jr. (Massachusetts General Hospital Cancer Center, Boston, MA, 02114, USA). Oncologist, 6(5), 407-414 (English) 2001. CODEN: OCOLF6. ISSN: 1083-7159. Publisher: AlphaMed Press.

AB A review. Is any one combination therapy for metastatic non-small cell lung **cancer** (NSCLC) superior to other regimens for metastatic NSCLC. The answer is "probably number". More than 4000 patients with advanced NSCLC participated in randomized trials presented at the 37th Annual Meeting of the American Society of Clin. Oncol. TAX326 was the only study in which the investigational arm (cisplatin/docetaxel) showed a statistically significant difference in survival compared with the reference standard (cisplatin/vinorelbine). The authors did learn, however, that what is administered may make some difference: cisplatin might be superior to carboplatin, and patients treated with nonplatinum chemotherapy regimens have a trend toward poorer survival than those who receive platinum doublets. Although there is still no clear best regimen for advanced NSCLC, doctors may now know how much chemotherapy to give: a randomized study presented found that four cycles produces as much survival benefit as treating until progression. The most significant abstrs. presented at this year's lung **cancer** session involved the use of novel agents with unique mechanisms of action. The median survival in the large, randomized trials of chemotherapy in advanced NSCLC remains a bleak 9 mo. ISIS 3521, an antisense oligonucleotide that targets protein kinase C, was found to produce a near doubling of survival when combined with carboplatin and paclitaxel. OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, was shown to have impressive single agent activity in the second-line treatment of lung **cancer**. The future of lung **cancer** therapy will involve combining these novel agents with active chemotherapy regimens in an effort to improve outcome. While it appears that a plateau has been reached in what can be accomplished with various combinations of cytotoxic chemotherapy in metastatic NSCLC, in locally-advanced disease new chemotherapy combinations can achieve remarkable results when combined with radiation therapy. The Southwest Oncol. Group presented unprecedented phase II data on the use of cisplatin and etoposide with concurrent radiation therapy followed by consolidation docetaxel in patients with stage IIIB NSCLC.

L8 ANSWER 4 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2001:799777 Document No. 137:27578 A novel approach in the treatment of **cancer**: Targeting the epidermal growth factor receptor. Ciardiello, Fortunato; Tortora, Giampaolo (Cattedra di Oncologia Medica. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli "Federico II,", Naples, 80131, Italy). Clinical Cancer Research, 7(10), 2958-2970 (English) 2001. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.

AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to **cancer** development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in **cancer** has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to **cancer** therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR.

Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in **cancer** patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A number of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

L8 ANSWER 5 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2001:746944 Document No. 136:144431 Targeting the epidermal growth factor receptor: a clinical reality. Baselga, Jose (Vall d'Hebron University Hospital, Barcelona, 08035, Spain). Journal of Clinical Oncology, 19(18, Suppl.), 41s-44s (English) 2001. CODEN: JCONDN. ISSN: 0732-183X. Publisher: Lippincott Williams & Wilkins.
AB A review presents four studies which further establishes the potential of epidermal growth factor (EGF) receptor as a target for **cancer** therapy. A novel EGF receptor tyrosine kinase inhibitor, OSI-774, has antitumor activity against several tumor types. The EGF receptor monoclonal antibody IMC-C225 reverses clin. chemotherapy resistance in colorectal carcinoma. The selective EGT receptor tyrosine kinase inhibitor, ZD1839, prevents activation of HER2 and has antitumor activity alone and in combination with trastuzumab in breast carcinoma cell lines.

L8 ANSWER 6 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2001:696814 Document No. 136:65 Ovarian **cancer**. Seiden, Michael V. (Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, 02114, USA). Oncologist, 6(4), 327-332 (English) 2001. CODEN: OCOLF6. ISSN: 1083-7159. Publisher: AlphaMed Press.
AB A review. Ovarian **cancer** remains the most lethal gynecol. malignancy in women in the United States. Studies from this year's American Society of Clin. Oncol. more clearly defined the role of chemotherapy in women with early stage disease and now suggest that essentially all women with invasive disease should receive chemotherapy that contains carboplatin. Studies in women with advanced disease continue to support the use of carboplatin and paclitaxel in the treatment of women with newly diagnosed disease although early data suggest that carboplatin and docetaxel might be an acceptable alternative. Platinum-resistant disease remains a therapeutic challenge. Small mols. that inhibit the function of the epidermal growth factor receptor, such as OSI-774, and novel classes of chemotherapeutic agents, including the acylfulvene MGI-114 and epothilone B and its analog, BMS247550, all warrant further study in this disease.

L8 ANSWER 7 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2001:160743 Document No. 135:189476 OSI-774 OSI Pharmaceuticals. Norman, Peter (Norman Consulting, Bucks, SL1 8JW, UK). Current Opinion in Investigational Drugs (PharmaPress Ltd.), 2(2), 298-304 (English) 2001. CODEN: COIDAZ. Publisher: PharmaPress Ltd..
AB A review with many refs. OSI-774 (formerly CP-358774), a quinazoline derivative, is an orally active epidermal growth factor receptor (EGFR) inhibitor which was originally under joint development by Pfizer and OSI Pharmaceuticals (formerly Oncogene Science) for the potential treatment of

cancer (eg, ovarian, non-small cell lung **cancer** (NSCLC) and head and neck). It is being in phase II trials. On 8 Jan. 2001, OSI announced that it had signed an agreement with Roche and Genentech for the global co-development and marketing of OSI-774. The agreement with Genentech covers the United States, that with Roche the rest of the world. In June 2000, OSI gained all development and marketing rights for OSI-774 following Pfizer's merger with Warner-Lambert. In Sept. 2000, Pfizer transferred the IND dossier for OSI-774 to OSI ahead of the time-line agreed in the June 2000 development and marketing rights agreement. The phase II trials will assess OSI-774 both as a single agent and in combination with existing chemotherapy regimens. Phase III trials are expected to be initiated in 2001. In Octoer 2000, Lehman Brothers predicted that OSI-774 would move into pivotal trials in the first half of 2001 and that the drug would be launched in 2003. The analysts also estimated worldwide sales of US $66 million, $85 million and $461 million in 2003, 2004 and 2005, resp., and peak sales in excess of US $500 million.

L8 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:81360 Document No. 139:190360 Erlotinib hydrochloride: oncolytic EGF receptor inhibitor. Sorbera, L. A.; Castaner, J.; Silvestre, J. S.; Bayes, M. (Prous Science, Barcelona, 08080, Spain). Drugs of the Future, 27(10), 923-934 (English) 2002. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.
AB A review. The epidermal growth factor receptor (EGFR) is a type 1 receptor tyrosine kinase that is involved in the modulation of cellular differentiation and is overexpressed in many types of human cancers such as lung, pancreatic, ovarian, renal cell, gastric, hepatocellular and breast. Overexpression of EGFR is frequently correlated with increased tumor grade, increased metastatic potential and poor prognosis. Thus, inhibition of EGFR signaling is an attractive therapeutic option for the treatment of **cancer**. One method that can interfere with EGFR is the direct inhibition of EGFR tyrosine kinase activity. Several tyrosine kinase inhibitors have been developed and evaluated over the past 10 yr of which the majority are reversible competitors with ATP for binding to the intracellular catalytic domain of the tyrosine kinase. One such EGFR tyrosine kinase inhibitor that has shown excellent antitumor activity is erlotinib hydrochloride, an oral quinazoline derivative that reversibly and selectively inhibits tyrosine kinase activity.

L8 ANSWER 9 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:57578 Document No. 139:46544 Effects of the epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Ng, Sylvia S. W.; Tsao, Ming-Sound; Nicklee, Trudey; Hedley, David W. (Divisions of Experimental Therapeutics, Ontario Cancer Institute, Medical Biophysics, Princess Margaret Hospital and University of Toronto, Toronto, ON, M5G 2M9, Can.). Molecular Cancer Therapeutics, 1(10), 777-783 (English) 2002. CODEN: MCTOCF. ISSN: 1535-7163. Publisher: American Association for Cancer Research.
AB Pancreatic **cancer** is the fifth leading cause of **cancer** death in North America. Gemcitabine improves the quality of life of patients but fails to significantly reduce mortality. Our laboratory has demonstrated previously that the phosphatidylinositol 3'-kinase inhibitor wortmannin promotes gemcitabine antitumor. The present study examined the effects of the epidermal growth factor receptor (EGFR) inhibitor OSI-774 ("Tarceva") alone and in combination with wortmannin and/or gemcitabine on downstream signaling mols., as well as apoptosis in primary pancreatic **cancer** xenografts implanted orthotopicaly in severely combined

immunodeficient mice. Tumors established from two pancreatic **cancer** patients [Ontario **Cancer** Institute Pancreas number (OCIP#) 2 and OCIP#7] were treated with various combinations of the above three drugs and harvested for analyses of the following: the levels of phosphorylated and nonphosphorylated forms of EGFR, protein kinase B (PKB/Akt) and extracellular-regulated kinase (ERK1/2), and the extent of apoptosis using immunofluorescence image anal. and TUNEL assay, resp. OSI-774 alone significantly inhibited phosphorylation of EGFR in both of the primary xenografts. Phosphorylation of pERK decreased in OCIP#2, but not in OCIP#7. No significant effects on pPKB because of OSI-774 were observed in either tumor type. The extent of apoptosis was significantly increased by 2-fold in OCIP#2 tumors treated with gemcitabine and wortmannin in combination; an addnl. 2-fold increase in apoptosis was evident in the presence of OSI-774. Although wortmannin failed to enhance gemcitabine-induced apoptosis in OCIP#7 tumors, the extent of apoptosis was significantly increased with the inclusion of OSI-774 in the combination. Taken together, these findings support the use of OSI-774 plus a phosphatidylinositol 3'-kinase inhibitor in combination with gemcitabine in the treatment of pancreatic **cancer**.

L8 ANSWER 10 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2002:825213 Document No. 138:361940 Targeting the epidermal growth factor receptor for **cancer** therapy. Mendelsohn, John (University of Texas M.D. Anderson Cancer Center, Houston, TX, USA). Journal of Clinical Oncology, 20(18, Suppl.), 1s-13s (English) 2002. CODEN: JCONDN. ISSN: 0732-183X. Publisher: Lippincott Williams & Wilkins.
AB A review. A monoclonal antibody that binds to epidermal growth factor (EGF) receptors and that can block the binding of either EGF or transforming growth factor-alpha (TGF-α) might prevent cell proliferation by inhibiting the signal transduction pathways that depend on activation of the EGF receptor. The author discusses the rationale behind this hypothesis and focus on examples of research findings with three low-mol.-weight, soluble mols. that act on the EGF receptor ZD1839, OSI-774 and C225, including mechanisms of action and results from clin. trials.

L8 ANSWER 11 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2002:757182 Document No. 138:313642 Why the epidermal growth factor receptor? The rationale for **cancer** therapy. Baselga, Jose (Medical Oncology Service, Hospital Universitari Vall d'Hebron, Barcelona, Spain). Oncologist, 7(Suppl. 4), 2-8 (English) 2002. CODEN: OCOLF6. ISSN: 1083-7159. Publisher: AlphaMed Press.
AB A review. There is a need for new, selective anticancer agents that differentiate between malignant and non-malignant cells. The benefits of such agents would include a higher therapeutic index and lower toxicity than conventional therapies. Although expressed in non-malignant cells, the epidermal growth factor receptor (EGFR) is highly expressed in a variety of tumors, and its expression correlates with poor response to treatment, disease progression, and poor survival. Evidence for a role for the EGFR in the inhibition and pathogenesis of various cancers has led to the rationale design and development of agents that selectively target this receptor. Activation of the EGFR signaling pathway in **cancer** cells has been linked with increased cell proliferation, angiogenesis, and metastasis, and decreased apoptosis. Preclin. data show that anti-EGFR therapies can inhibit these effects in vitro and in vivo. In addition, preclin. data confirm that many such agents have the potential to increase the effectiveness of current cytotoxic agents. Following accelerated drug development programs, phase III trials are now under way for a number of

EGFR-targeted therapies, including the monoclonal antibody IMC-C225 and the EGFR-tyrosine kinase inhibitors ZD1839 (Iressa) and OSI-774. Thus, the rationale for EGFR-targeted approaches to **cancer** treatment is apparent and now well established, and there is increasing evidence that they may represent a significant contribution to **cancer** therapy.

L8 ANSWER 12 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2002:604225 Document No. 138:162767 EGF signal transduction and its molecular targeted drugs against **cancer**. Sone, Saburo; Yamamoto, Akihiko (Dep. Internal Med. Molecular Therapeutics, Univ. Tokushima Sch. Med., Japan). Saishin Igaku, 57(7), 1712-1717 (Japanese) 2002. CODEN: SAIGAK. ISSN: 0370-8241. Publisher: Saishin Igakusha.
AB A review. The epidermal growth factor receptor (EGFR) and its inhibition in **cancer** therapy is reviewed together with the mechanism related to EGF signal transduction of antitumor agents such as EGFR antibody (C225) and EGFR tyrosine kinase inhibitors (ZD1839, OSI-774, and CI-1033).

L8 ANSWER 13 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2004:335709 Preclinical studies with erlotinib (Tarceva). [Erratum to document cited in CA140:052547]. Akita, Robert W.; Sliwkowski, Mark X. (Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, USA). Seminars in Oncology, 30(6), 826 (English) 2003. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..
AB A review. An erratum.

L8 ANSWER 14 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2004:47341 Document No. 141:33137 Epidermal growth factor receptor-targeted therapy and symptom improvement in non-small cell lung **cancer**. Bonomi, Philip D. (Section of Medical Oncology, Rush University Medical Center, Chicago, IL, 60612, USA). American Journal of Health-System Pharmacy, 60(Suppl. 9), S16-S21 (English) 2003. CODEN: AHSPEK. ISSN: 1079-2082. Publisher: American Society of Health-System Pharmacists.
AB A review. Epidermal growth factor receptor-targeted therapy and symptom improvement in non-small cell lung **cancer** are discussed. Non-small cell lung **cancer** (NSCLC) is a common and frequently incurable disease. Patients with advanced stage IIIB/IV disease, although not candidates for curative resection, can benefit from treatment that prolongs survival, alleviates symptoms, and reduces complications. While incremental advances have occurred with the use of chemotherapy and radiation therapy, the benefits have been largely palliative. Moreover, the adverse events associated with these therapies may undermine the treatment goal by replacing disease-related symptoms with treatment-related adverse events. Thus, novel, more targeted approaches are needed. Increased understanding of cellular and mol. biol. has resulted in the development of treatments that selectively target key regulatory pathways and mols. involved in cell growth and metastasis. Gefitinib is one member of a new class of targeted anticancer agents known as tyrosine kinase inhibitors with activity against NSCLC. In clin. trials, gefitinib has produced responses in patients with relapsed or refractory NSCLC, reduced disease-related symptoms, and has been associated with improvements in quality of life. Such targeted therapy may have a significant impact on the treatment of patients with NSCLC.

L8 ANSWER 15 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2004:31795 Document No. 140:70157 Epidermal growth factor receptor tyrosine kinase inhibitors in late stage clinical trials. Ciardiello, Fortunato;

De Vita, Ferdinando; Orditura, Michele; De Placido, Sabino; Tortora, Giampaolo (Cattedra di Oncologia Medica, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale 'F Magrassi e A Lanzara, Seconda Universita degli Studi di Napoli, Naples, Italy). Expert Opinion on Emerging Drugs, 8(2), 501-514 (English) 2003. CODEN: EOEDA3. Publisher: Ashley Publications Ltd..

AB A review. The epidermal growth factor receptor (EGFR) is a cell membrane receptor that plays a key role in **cancer** development and progression. Ligand-activated EGFR-dependent signaling is involved in cell proliferation, apoptosis, angiogenesis and metastatic spread. Targeting the EGFR, therefore, represents a promising mol. approach in **cancer** treatment. Several anti-EGFR agents are in clin. development. Three drugs are currently in Phase II and III development as single agents, or in combination with other anticancer modalities: IMC-225 (cetuximab/Erbitux; ImClone), a chimeric human-mouse monoclonal IgG1 antibody, which blocks ligand binding and functional activation of the EGFR; OSI-774 (erlotinib/Tarceva; Genentech/OSI/Roch) and ZD1839 (gefitinib/Iressa; AstraZeneca), two small mol. EGFR-selective inhibitors of tyrosine kinase enzymic activity, which prevent EGFR autophosphorylation and activation. Iressa is the first EGFR-targeting agent to be registered as an anticancer drug in Japan, in Australia and in the US for the third-line treatment of chemoresistant non-small cell lung **cancer** (NSCLC) patients. This review will focus on the preclin. background and on the results from the first series of clin. trials with these drugs. Furthermore, continuing clin. trials and a series of open clin. issues for the development of optimal strategies of using EGFR-targeting agents will be discussed.

L8 ANSWER 16 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2003:825337 Document No. 139:345184 Development of the epidermal growth factor receptor inhibitor Tarceva (OSI-774). Gruenwald, Viktor; Hidalgo, Manuel (The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, 21231-1000, USA). Advances in Experimental Medicine and Biology, 532(New Trends in Cancer for the 21st Century), 235-246 (English) 2003. CODEN: AEMBAP. ISSN: 0065-2598. Publisher: Kluwer Academic/Plenum Publishers.

AB A review. The epidermal growth factor receptor (EGFR) is a transmembrane receptor involved in the regulation of a complex array of essential biol. processes such as cell proliferation and survival. Dysregulation of EGFR signaling network has been frequently reported in multiple human cancers and has been associated with the processes of tumor development, growth, proliferation, metastasis and angiogenesis. Inhibition of the EGFR was associated with antitumor effects in preclin. models. On the bases of these data, therapeutics targeting the EGFR were explore in clin. trials. Tarceva (OSI-774, OSI Pharmaceuticals, Uniondale, NY) is a small mol. selective inhibitor of the EGFR tyrosine kinase (TK). In preclin. studies, Tarceva inhibited the phosphorylation of the EGFR in a dose and concentration dependent manner resulting in cell cycle arrest and induction of apoptosis. In in vivo studies, the agent caused tumor growth inhibition and shoved synergistic effects when combined with conventional chemotherapy. Subsequent single agent phase I studies and phase I studies in combination with chemotherapy demonstrated that the agent has a good safety profile and induced tumor growth inhibition in a substantial number of patients with a variety of different solid tumor. Preliminary report from phase II studies confirmed the excellent tolerability of Tarceva as well as showed encouraging preliminary activity. Phase III studies have either been completed or are ongoing in several tumor types such as lung **cancer** and pancreatic **cancer**. In summary, Tarceva is a

novel inhibitor of the EGFR TK which has shown promising activity in initial studies and is currently undergoing full development as an anticancer drug.

L8 ANSWER 17 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:695035 Document No. 140:104240 Epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung **cancer**. Fukuoka, Masahiro; Nakagawa, Kazuhiko (Department of Medical Oncology, Kinki University School of Medicine, Osaka, 589-8511, Japan). Biotherapy (Tokyo, Japan), 17(4), 346-351 (Japanese) 2003. CODEN: BITPE9. ISSN: 0914-2223. Publisher: Gan to Kagaku Ryohosha.
AB A review. EGFR tyrosine kinase inhibitors (EGFR-TKIs) are currently being developed as a **cancer** therapeutic agent. EGFR-TKI which has been performed clin. trials in non-small cell lung **cancer** (NSCLC) includes gefitinib (Iressa) and erlonitib (Tarceva). Two randomized double blind phase II trials of single agent gefitinib (IDEAL 1 and 2) have shown significant activity and tolerability in patients with previously treated NSCLC. Response rates were 18.4% on 250 mg/day and 19% on 500 mg/day in IDEAL 1, and 11.0% on 250 mg/day and 9.0% on 500 mg/day in IDEAL 2. Drug-related adverse events (AEs) in both trials were generally mild (grade 1/2), consisting mainly of skin reactions and diarrhea. Fewer patients on 250 mg/day gefitinib experienced drug-related grade 3 or 4 AEs compared with 500 mg/day. Severe acute interstitial lung disease does occur in association with gefitinib treatment. Phase III studies comparing standard chemotherapy (carboplatin/taxol and cisplatin/gemcitabine) and gefitinib with placebo have been conducted in patients with previously untreated NSCLC. These trials have shown that any differences are not observed between the gefitinib and the placebo groups. A single agent phase II trial of erlotinib has been conducted to assess the efficacy and safety of erlotinib in 57 patients with EGFR-pos. NSCLC who had failed prior platinum-based chemotherapy. All patients received erlotinib as a 150 mg/day orally for a maximum of 52 wk, or until disease progression or unmanageable toxicity. Of the 57 patients, two achieved a CR and five had a PR, resulting in an overall RR of 12.3%. The most common rash and/or diarrhea occurred as single events or concurrently in 90% of the patients. Grade 3 events occurring in 2 patients (4%) each were: dysphagia, pruritus, fatigue, and dyspnea. Only one patient had grade 3 diarrhea. In conclusion, single agent activity of gefitinib or erlotinib in terms of response and survival data, as well as the lack of severe toxicities commonly associated with cytotoxic chemotherapy, indicate that the EGFR-TKI has a favorable risk-to-benefit ratio for the treatment of patients with advanced NSCLC whose disease has progressed or relapsed following platinum-based chemotherapy.

L8 ANSWER 18 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:682016 Document No. 140:209642 Molecular target-based **cancer** therapy: tyrosine kinase inhibitors. Tamura, Kenji; Fukuoka, Masahiro (Department of Medical Oncology, Kinki University School of Medicine, Osaka, 589-8511, Japan). International Journal of Clinical Oncology, 8(4), 207-211 (English) 2003. CODEN: IJCOF6. ISSN: 1341-9625. Publisher: Springer-Verlag Tokyo.
AB A review. Improved understanding of tumor biol. has led to the identification of numerous growth factors that are involved in malignant transformation and tumor progression. Many of these factors induce cellular responses through receptors with intrinsic tyrosine kinase (TK) activity. Therefore, inhibiting the activity of TK receptors is one of the ways to effectively block the disordered proliferation of **cancer** that arises from these pathways. The human epidermal

growth factor receptor (HER) family is overexpressed or dysfunctional in many human malignancies. Therefore, these receptors have been identified as targets for **cancer** therapy. Several agents have been developed that reversibly or irreversibly inhibit one, two, or all of the HER receptors. Iressa and Tarceva are HER1-specific TK inhibitors that are in advanced development. The large phase II study of Iressa (IDEAL1) in patients with non-small-cell lung **cancer** (NSCLC) in whom previous platinum-based therapy has failed, found that the median survival time (MST) was 7.6 mo, which was no less than that with Docetaxel treatment. Other dual or pan-HER, reversible or irreversible, TK inhibitors are being investigated in phase I trials. Early data show that they are generally well tolerated and have provided evidence of against activity tumors. HER-TK inhibitors are likely to have a substantial impact on the treatment of **cancer** patients.

L8 ANSWER 19 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:640503 Document No. 140:52547 Preclinical studies with erlotinib (Tarceva). Akita, Robert W.; Sliwkowski, Mark X. (Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, USA). Seminars in Oncology, 30(3, Suppl. 7), 15-24 (English) 2003. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..
AB A review. Erlotinib HCI (Tarceva; Genentech, Inc, South San Francisco, CA) is an orally available, highly selective, reversible inhibitor of epidermal growth factor receptor (HER1/EGFR) tyrosine kinase. Inhibition of tyrosine kinase activity prevents HER1/EGFR phosphorylation, the associated downstream signaling events, and may block tumorigenesis mediated by inappropriate HER1/EGFR signaling. In vitro and in vivo studies show that erlotinib has activity against human colorectal, head and neck, non-small cell lung, and pancreatic tumor cells. Recent preclin. studies suggest that erlotinib may also have activity against tumors that are dependent on HER2 activation for growth and/or survival. Preclin. studies have addressed the feasibility of using erlotinib in combination with various chemotherapeutic agents, radiotherapy, and targeted agents. Combining agents that have different mechanisms of action has the potential to improve efficacy and inhibit the development of resistance. For example, in preclin. studies, combining erlotinib with cisplatin, doxorubicin, gemcitabine, or low-dose paclitaxel has an additive effect on antitumor activity with no increase in toxicity. Preclin. data provide a strong rationale for investigating erlotinib in the clin. setting. However, addnl. studies are required to gain further insights into the processes that regulate or influence the antitumor activity of erlotinib.

L8 ANSWER 20 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:613804 Document No. 140:52925 The biological and biochemical effects of CP-654577, a selective erbB2 kinase inhibitor, on human breast **cancer** cells. Barbacci, E. Gabriella; Pustilnik, Leslie R.; Rossi, Ann Marie K.; Emerson, Erling; Miller, Penny E.; Boscoe, Brian P.; Cox, Eric D.; Iwata, Kenneth K.; Jani, Jitesh P.; Provoncha, Kathleen; Kath, John C.; Liu, Zhengyu; Moyer, James D. (Pfizer Global Research and Development, Groton, CT, 06340, USA). Cancer Research, 63(15), 4450-4459 (English) 2003. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.
AB Aberrant expression or activity of epidermal growth factor receptor (EGFr) or the closely related p185erbB2 can promote cell proliferation and survival and thereby contribute to tumorigenesis. Specific antibodies and low mol.-weight tyrosine kinase inhibitors of both proteins are in clin. trials for **cancer** treatment. CP-654577 is a potent inhibitor selective for p185erbB2, relative to EGFr tyrosine kinase, and selectively

reduces erbB2 autophosphorylation in intact cells. Treatment of SKBr3 human breast **cancer** cells with CP-654577 reduces the levels of the activated form of mitogen-activated protein kinase, increases the levels of cyclin-dependent kinase inhibitor p27kip1 and reduces expression of cyclins D and E. These biochem. changes result in a reduced level of phosphorylated retinoblastoma protein and an inhibition of cell-cycle progression at G1. Apoptosis is triggered in both SKBr3 and another high erbB2-expressing cell line, BT474, by exposure to 1 μM CP-654577, but this effect is not observed in MCF7 cells that express low erbB2. Levels of activated Akt, an important pos. regulator of cell survival, are reduced within 2 h of exposure to 250 nM CP-654577, and this may contribute to the increased apoptosis. These biochem. effects are distinct from those produced by Tarceva, a selective EGFr inhibitor. The antitumor activity of CP-654577 was investigated in athymic mice bearing s.c. tumors from Fischer rat embryo fibroblasts transfected with erbB2. CP-654577 produced a dose-dependent reduction of p185erbB2 autophosphorylation and inhibited the growth of these tumors. CP-654577 warrants further evaluation in tumors with high expression of p185erbB2 and may differ from selective EGFr inhibitors or nonselective dual EGFr/erbB2 inhibitors in efficacy and therapeutic index.

L8 ANSWER 21 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:553651 Document No. 139:190525 Development of the epidermal growth factor receptor inhibitor OSI-774. Grunwald, Viktor; Hidalgo, Manuel (The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA). Seminars in Oncology, 30(3, Suppl. 6), 23-31 (English) 2003. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..

AB A review. The epidermal growth factor receptor (EGFR) is a transmembrane receptor involved in the regulation of a complex array of essential biol. processes such as cell proliferation and survival. Dysregulation of the EGFR signaling network has been frequently reported in multiple human cancers and has been associated with the processes of tumor development, growth, proliferation, metastasis, and angiogenesis. Inhibition of the EGFR was associated with antitumor effects in preclin. models. On the basis of these data, therapeutics targeting the EGFR were explored in clin. trials. OSI-774 is a small-mol. selective inhibitor of the EGFR tyrosine kinase. In.preclin. studies, OSI-774 inhibited the phosphorylation of the EGFR in a dose-dependent and concentration-dependent manner resulting in cell cycle arrest and induction of apoptosis. In in vivo studies, this agent caused tumor growth inhibition and showed synergistic effects when combined with conventional chemotherapy. Subsequent single-agent phase I studies and phase I, studies in combination with chemotherapy showed that the agent has a good safety profile and induced tumor growth inhibition in a substantial number of patients with a variety of different solid tumors. Preliminary reports from phase II studies confirmed the excellent tolerability of OSI-774 and showed encouraging preliminary activity. Phase III studies have either been completed or are ongoing in several tumor types such as lung **cancer** and pancreatic **cancer**. In summary, OSI-774 is a novel inhibitor of the EGFR tyrosine kinase that has shown promising activity in initial studies and is currently undergoing full development as an anticancer drug.

L8 ANSWER 22 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:543288 Document No. 139:190493 Erlotinib (Tarceva): a promising drug targeting epidermal growth factor receptor tyrosine kinase. Bulgaru, Anca M.; Mani, Sridhar; Goel, Sanjay; Perez-Soler, Roman (Department of Oncology, Montefiore Medical Center, Bronx, NY, 10467, USA). Expert Review of Anticancer Therapy, 3(3), 269-279 (English) 2003. CODEN:

ERATBJ. ISSN: 1473-7140. Publisher: Future Drugs Ltd..

AB A review. Overexpression of the epidermal growth factor receptor (EGFR) is correlated with a poor prognosis in several human malignancies. In addition, cancers overexpressing EGFR respond poorly to both chemotherapy and radiation therapy. Therefore, EGFR is a viable target for **cancer** therapy. This review will address how EGFR blockade modulates signal transduction, leading to alterations in the cell cycle progression with secondary inhibition of proliferation and differentiation of **cancer** cells. As a prototypical example, edofinib (Tarceva), a reversible EGFR tyrosine kinase inhibitor will be discussed. This drug has demonstrated promising antitumor activity in Phase II trials in several solid tumors and definitive Phase III studies to demonstrate clin. benefit have completed accrual.

L8 ANSWER 23 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2003:528791 Document No. 140:52880 Pharmacodynamic Evaluation of the Epidermal Growth Factor Receptor Inhibitor OSI-774 in Human Epidermis of **Cancer** Patients. Malik, Shazli N.; Siu, Lillian L.; Rowinsky, Eric K.; de Graffenried, Linda; Hammond, Lisa A.; Rizzo, Jinee; Bacus, Sarah; Brattain, Michael G.; Kreisberg, Jeffrey I.; Hidalgo, Manuel (The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA). Clinical Cancer Research, 9(7), 2478-2486 (English) 2003. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.

AB BACKGROUND: OSI-774 is an inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK) currently in clin. development. In preclin. models, the antitumor activity of OSI-774 was directly related to its ability to inhibit the EGFR-TK. On the basis of these data, we hypothesized that inhibition of the EGFR-TK will be required for this agent to be effective in the clinic. This study evaluated the pharmacodynamic effects of OSI-774 in normal skin tissues collected from patients treated with the agent in a Phase I study. METHODS: Patients with advanced **cancer** who were treated in a Phase I study of OSI-774 underwent a biopsy of normal skin epidermis at baseline and after the last dose of drug in the first course of treatment. The expression and activation of the EGFR, downstream signaling extracytoplasmatic-regulated kinase (Erk), and cell cycle regulator p27 were determined in paraffin-embedded skin tissues using an immunohistochem. method (IHC). The IHC data were analyzed using both a semiquant. scoring system and an automatic absorbance quant. IHC method. The number of cells with nuclear staining of p27 per 500 cells was determined Plasma samples were collected to quantitate OSI-774 plasma concns. RESULTS: A total of 56 skin specimens was collected from 28 patients treated with OSI-774 at doses ranging from 25 to 200 mg/day. There was a significant decrease in phospho-EGFR (Tyr 1173) expression as determined semiquant. with OSI-774 treatment [2.75 ± 0.51 (mean ± SD) pretreatment vs. 2.36 ± 0.76 after treatment, pair comparison P = 0.01]. The quant. ratio [(phospho-EGFR/EGFR) x 100] of phospho-EGFR (Tyr1173) decreased from 64.16 ± 36.58 pretreatment to 48.87 ± 35.37 post-treatment (pair comparison, P = 0.02). No significant differences were observed in phospho-Erk (Thr202/Tyr204) expression. The mean number of cells with nuclear staining for p27 increased from 185 ± 101 (mean ± SD) pretreatment to 253 ± 111 post-treatment (pair comparison P = 0.02). A total of 12 (42.8%), 7 (25%), and 14 (50%) patients had >25% variation in the ratio of phospho-EGFR (Tyr1173), phospho-Erk (Thr202/Tyr204), and p27 expression, resp. Only changes in p27 expression were related to the administered dose of OSI-774. CONCLUSIONS: OSI-774 exerted pharmacodynamic effects in skin tissues of 30-50% of patients treated with the agent. Up-regulation

of p27, which is a downstream effect of EGFR inhibition, was dose related. Although there was a significant decrement in phospho-EGFR (Tyr1173), it was not related to the administered dose of OSI-774. On the basis of these findings and the relatively simple and reliable method to measure p27 expression, this biomarker appears to be the most promising and is being evaluated in Phase II studies as a predictor of clin. outcome.

L8 ANSWER 24 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:442265 Document No. 139:373873 Target-based agents against ErbB receptors and their ligands: A novel approach to **cancer** treatment. Normanno, N.; Bianco, C.; De Luca, A.; Maiello, M. R.; Salomon, D. S. (Division of Hematological Oncology and Department of Experimental Oncology, INT-Fondazione Pascale, Naples, 80131, Italy). Endocrine-Related Cancer, 10(1), 1-21 (English) 2003. CODEN: ERCAE9. ISSN: 1351-0088. Publisher: Society for Endocrinology.
AB A review. The ErbB receptors and their cognate ligands that belong to the epidermal growth factor (EGF) family of peptides are involved in the pathogenesis of different types of carcinomas. In fact, the ErbB receptors and the EGF-like growth factors are frequently expressed in human tumors. These proteins form a complex system that regulates the proliferation and the survival of **cancer** cells. Therefore, ErbB receptors and their ligands might represent suitable targets for novel therapeutic approaches in human carcinomas. In this regard, different target-based agents that are directed against the ErbB receptors have been developed in the past two decades. One of these compds., the humanized anti-ErbB-2 monoclonal antibody trastuzumab has been approved for the treatment of patients with metastatic breast **cancer**. The anti-EGF receptor (EGFR) antibody C225, as well as EGFR tyrosine kinase inhibitors ZD1839 and OSI-774 are currently in phase III clin. development. Several other ErbB tyrosine kinase inhibitors are in phase I/II studies. These compds. have generally been shown to have an acceptable toxicity profile and promising antitumor activity in heavily pretreated patients. The mechanisms of action of these compds., as well as the potential therapeutic strategies to improve their efficacy are discussed in this review with particular regard to the combinations of anti-ErbB agents with cytotoxic drugs, or combinations of different ErbB-targeting agents.

L8 ANSWER 25 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2003:252600 Document No. 139:275243 Epidermal growth factor receptor as a therapeutic target in colorectal **cancer**. Cohen, Roger B. (Fox Chase Cancer Center, Philadelphia, PA, USA). Clinical Colorectal Cancer, 2(4), 246-251 (English) 2003. CODEN: CCCLCF. ISSN: 1533-0028. Publisher: Cancer Information Group.
AB A review. The epidermal growth factor receptor (EGFR) is widely expressed in advanced colorectal cancers (CRCs), and higher levels of EGFR are inversely related to survival in these patients. Two general strategies have been used to block EGFR signaling: preventing ligand binding with anti-EGFR monoclonal antibodies (eg, cetuximab and ABX-EGF) and inhibiting its intrinsic tyrosine kinase with small mols. (eg, gefitinib [Iressa] and erlotinib [OSI-774,Tarceva]). Phase II trials of cetuximab suggest that it might be an effective treatment option alone or in combination with standard therapies as first- or second-line therapy. Phase I studies evaluating other EGFR inhibitors in patients with CRC have been reported. The inclusion of anti-EGFR therapies into standard treatment is the subject of current clin. trials.

L8 ANSWER 26 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2003:211937 Document No. 139:78226 Signal transduction-directed **cancer** treatments. Sausville, Edward A.; Elsayed, Yusri; Monga, Manish; Kim, George (Developmental Therapeutics Program, National Cancer Institute, Rockville, MD, 20852, USA). Annual Review of Pharmacology and Toxicology, 43, 199-231 (English) 2003. CODEN: ARPTDI. ISSN: 0362-1642. Publisher: Annual Reviews Inc..

AB A review. The pathogenic mechanisms giving rise to **cancer** frequently involve altered signal transduction pathways. Therefore therapeutic agents that directly address signal transduction mols. are being explored as **cancer** treatments. Inhibitors of protein tyrosine and threonine kinases including STI-571, ZD-1839, OSI-774, and flavopiridol are ATP-site antagonists that have completed initial phase I and phase II evaluations. Herceptin and C225 are monoclonal antibodies also directed against signaling targets. Numerous other kinase antagonists are in clin. evaluation, including UCN-01 and PD184352. Alternative strategies to downmodulate kinase-driven signaling include 17-allyl-amino-17-demethoxygeldanamycin and rapamycin derivs., and phospholipase-directed signaling may be modulated by alkylphospholipids. Farnesyltransferase inhibitors were originally developed as inhibitors of ras-driven signals but may have activity by affecting other or addnl. targets. Signal transduction will remain a fertile basis for suggesting **cancer** treatments of the future, the evaluation of which should include monitoring effects of the drugs on their intended target signaling mols. in preclin. and early clin. studies.

L8 ANSWER 27 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2003:39629 Document No. 138:269401 ERBB2 Up-Regulates S100A4 and Several other Prometastatic Genes in Medulloblastoma. Hernan, Roberto; Fasheh, Rami; Calabrese, Christopher; Frank, Adrian J.; Maclean, Kirsteen H.; Allard, David; Barraclough, Roger; Gilbertson, Richard J. (Life Sciences Building, and School of Biological Sciences, Tennessee 38105, Memphis, St. Jude Children's Research Hospital, Departments of Developmental Neurobiology and Biochemistry, University of Liverpool, Liverpool, L69 7ZB, UK). Cancer Research, 63(1), 140-148 (English) 2003. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Medulloblastoma is frequently disseminated throughout the central nervous system by the time of diagnosis. Conventional therapeutic approaches have not reduced the high mortality associated with metastatic medulloblastoma and little is known regarding the mol. mechanisms that promote tumor invasion. Previously, we reported that overexpression of ERBB2 in medulloblastoma is associated with poor prognosis and metastasis. Here, we demonstrate that ERBB2 overexpression increases the migration of medulloblastoma cells across basement membranes in vitro. Furthermore, using microarray expression profiling, we show that ERBB2 up-regulates the expression of prometastatic genes in medulloblastoma cells. These include S100A4, which was previously shown to promote metastasis of breast **cancer**. We demonstrate that S100A4 is a direct target of ERBB2 signaling in medulloblastoma cells via a pathway involving phosphatidylinositol 3-kinase, AKT1, and extracellular signal-regulated kinase 1/2 and that levels of ERBB2 and S100A4 are tightly correlated in samples of primary medulloblastoma. Finally, we show that ERBB2-dependent medulloblastoma cell invasion in vitro and prometastatic gene expression in vivo can be blocked using the ERBB tyrosine kinase inhibitor OSI-774. These data identify an ERBB2 driven prometastatic pathway that may provide a novel target for therapeutic intervention in metastatic medulloblastoma.

L8 ANSWER 28 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2003:8967 Document No. 139:62338 Small molecule tyrosine kinase inhibitors:

clinical development of anticancer agents. Laird, A. Douglas; Cherrington, Julie M. (SUGEN, Inc., South San Francisco, CA, 94080, USA). Expert Opinion on Investigational Drugs, 12(1), 51-64 (English) 2003. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications Ltd..

AB A review. Numerous small mol. synthetic tyrosine kinase inhibitors are in clin. development for the treatment of human cancers. These fall into three broad categories: inhibitors of the epidermal growth factor receptor tyrosine kinase family (e.g., Iressa and Tarceva), inhibitors of the split kinase domain receptor tyrosine kinase subgroup (e.g., PTK787/ZK 222584 and SU11248) and inhibitors of tyrosine kinases from multiple subgroups (e.g., Gleevec). In addition, agents targeting other tyrosine kinases implicated in **cancer**, such as Met, Tie-2 and Src, are in preclin. development. As experience is gained in the clinic, it has become clear that unleashing the full therapeutic potential of tyrosine kinase inhibitors will require patient preselection, better assays to guide dose selection, knowledge of mechanism-based side effects and ways to predict and overcome drug resistance.

L8 ANSWER 29 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2002:974164 Document No. 139:143003 Clinical evaluation of agents targeting epidermal growth factor receptor (EGFR) in **cancer**. Lin, Edward H.; Abbruzzese, James L. (Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA). Oncogene-Directed Therapies, 313-330. Editor(s): Rak, Janusz. Humana Press Inc.: Totowa, N. J. ISBN: 0-89603-982-X (English) 2003. CODEN: 69DKTX.

AB A review. Proteins encoded by oncogenes and tumor-suppressor genes are the essential signaling components of the complex cellular signaling networks. **Cancer** arises from a multi-step process promoted by the imbalanced growth signals as a consequence of gain of oncogene and/or loss of tumor suppressor genes. The six essential **cancer** hallmarks include persistent cell growth signals, insensitivity to anti-growth signals, evasion of apoptosis, persistent angiogenesis, gain of cell immortality, and tumor invasion and metastasis. As an oncogene, gain of epidermal growth factor receptor (EGFR) function is achieved through EGFR over-expression and has been shown to be associated with almost all the six essential hallmarks of **cancer** except the gain of cell immortality. In various exptl. models, EGFR inhibition leads to regression of tumor cell growth, inhibition of angiogenesis, induction of apoptosis, and inhibition of tumor invasion and metastasis. Furthermore, over-expression of EGFR, frequently observed in a number of human cancers, is associated with poor overall prognosis, increased tumor recurrence, and decreased patient survival. The hypothesis that EGFR might be a **cancer** therapeutic target was proposed by Mendelsohn in the early 1980s; emerging only recently are the promising clin. trial results from a number of EGFR antagonists in different human cancers. This review will discuss the clin. developments and future directions of EGFR antagonists in **cancer** treatment.

L8 ANSWER 30 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2004:432009 Document No. 141:684 Antitumor activity of erlotinib (OSI-774, Tarceva) alone or in combination in human non-small cell lung **cancer** tumor xenograft models. Higgins, Brian; Kolinsky, Kenneth; Smith, Melissa; Beck, Gordon; Rashed, Mohammad; Adames, Violeta; Linn, Michael; Wheeldon, Eric; Gand, Laurent; Birnboeck, Herbert; Hoffmann, Gerhard (Department of Oncology, In Vivo Section, Hoffmann-La Roche Inc, Nutley, NJ, USA). Anti-Cancer Drugs, 15(5), 503-512 (English) 2004. CODEN: ANTDEV. ISSN: 0959-4973. Publisher: Lippincott Williams &

Wilkins.

AB Our objective was the preclin. assessment of the pharmacokinetics, monotherapy, and combined antitumor activity of the epidermal growth factor receptor (HER1/EGFR) Tyr kinase inhibitor erlotinib in athymic nude mice bearing non-small cell lung **cancer** (NSCLC) xenograft models. Immunohistochem. determined the HER1/EGFR status of the NSCLC tumor models. Pharmacokinetic studies assessed blood plasma drug concns. of erlotinib in tumor- and non-tumor-bearing athymic nude mice. These were followed by maximum tolerated dose (MTD) studies for erlotinib and each chemotherapy. Erlotinib was then assessed alone and in combination with these chemotherapies in the NSCLC xenograft models. Complete necropsies were performed on most of the animals in each study to further assess antitumor or toxic effects. Erlotinib monotherapy dose-dependently inhibited tumor growth in the H460a tumor model, correlating with circulating levels of drug. There was antitumor activity at the MTD with each agent tested in both the H460a and A549 tumor models (erlotinib 100 mg/kg: 71 and 93% tumor growth inhibition; gemcitabine 120 mg/kg: 93 and 75% tumor growth inhibition; cisplatin 6 mg/kg: 81 and 88% tumor growth inhibition). When each compound was given at a fraction of the MTD, tumor growth inhibition was suboptimal. Combinations of gemcitabine or cisplatin with erlotinib were assessed at 25% of the MTD to determine efficacy. In both NSCLC models, doses of gemcitabine (30 mg/kg) or cisplatin (1.5 mg/kg) with erlotinib (25 mg/kg) at 25% of the MTD were well tolerated. For the slow growing A549 tumor, there was significant tumor growth inhibition in the gemcitabine/erlotinib and cisplatin/erlotinib combinations (above 100 and 98%, resp.), with partial regressions. For the faster growing H460a tumor, there was significant but less remarkable tumor growth inhibition in these same combinations (86 and 53% resp.). These results show that in NSCLC xenograft tumors with similar levels of EGFR expression, the antitumor activity of erlotinib is robust both as monotherapy and in combination with chemotherapies.

L8 ANSWER 31 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2004:387834 Document No. 140:368007 Rationale and clinical validation of epidermal growth factor receptor as a target in the treatment of head and neck **cancer**. Caponigro, Francesco (Instituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale", Naples, Italy). Anti-Cancer Drugs, 15(4), 311-320 (English) 2004. CODEN: ANTDEV. ISSN: 0959-4973. Publisher: Lippincott Williams & Wilkins.

AB A review. Recurrent/metastatic head and neck **cancer** is an area of high, unmet treatment need. There is a strong rationale for targeting the epidermal growth factor receptor (EGFR) in head and neck **cancer** as most of these tumors express high levels of EGFR relative to normal tissue, with high expression correlating with poor patient outcome. This rationale has been validated in extensive preclin. studies. Two small mols. with EGFR inhibitory activity, gefitinib ("Iressa", ZD1839) and erlotinib ("Tarceva", OSI-774), and a humanized monoclonal antibody against the EGFR extracellular domain, cetuximab ("Erbitux", C225), are in clin. trials for advanced head and neck **cancer**. The initial results of these trials are promising. Gefitinib and erlotinib show activity as monotherapy in patients with recurrent or metastatic head and neck **cancer**, and have an acceptable safety profile compared with conventional chemotherapy. Gefitinib, which can be given at doses below the maximum tolerated dose, is associated with slightly lower rates of adverse events than erlotinib, which is dosed at the maximum tolerated dose. Combinations of cetuximab with radiotherapy or platinum-based chemotherapy have also shown activity in phase I/II studies. Both gefitinib and cetuximab have entered phase III

studies. The results of these trials, which will mature over the next few years, will help determine the optimal use of EGFR agents in head and neck cancers.

L8 ANSWER 32 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2004:108293 Document No. 140:354496 The HER receptor family: a rich target for therapeutic development. Mass, Robert D. (Genentech BioOncology, Inc., South San Francisco, CA, 94080-4990, USA). International Journal of Radiation Oncology, Biology, Physics, 58(3), 932-940 (English) 2004. CODEN: IOBPD3. ISSN: 0360-3016. Publisher: Elsevier Science Inc..
AB A review. The key role of the HER family of receptors in **cancer** was widely acknowledged. HER receptor activation occurs via ligand binding or nonligand-dependent receptor dimerization, initiating signals that promote tumorigenesis via cell proliferation, survival, migration, adhesion, and differentiation. Therapeutic strategies designed to target and inhibit HER activation that are in clin. development are reviewed, including examples of both small-mol. tyrosine kinase inhibitors and monoclonal antibodies. Tarceva is a potent, highly selective, reversible inhibitor of HER1/epidermal growth factor receptor tyrosine kinase with inhibitory activity against various in vitro and in vivo models of solid human tumors. Phase II trials in refractory non-small-cell lung, head-and-neck, and ovarian **cancer** have demonstrated clin. activity, including objective responses and prolonged, stable disease. Four Phase III trials are ongoing evaluating primarily the effect on survival of Tarceva in combination with chemotherapy. 2C4 is a humanized anti-HER2 monoclonal antibody that binds to a broad, extracellular epitope, resulting in steric inhibition of HER-receptor complex formation that involves HER2. 2C4 has shown significant activity in xenograft models of prostate, lung, and breast **cancer**. 2C4's activity, unlike Herceptin's, is not dependent on HER2 amplification. This antibody is in early clin. development. The strategy of targeting the HER system was further validated by early experience with Tarceva and 2C4. The optimal clin. benefit of these agents will likely involve combinations of biol. agents, with or without traditional chemotherapy, and will be guided by critical predictive diagnostic information.

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RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)
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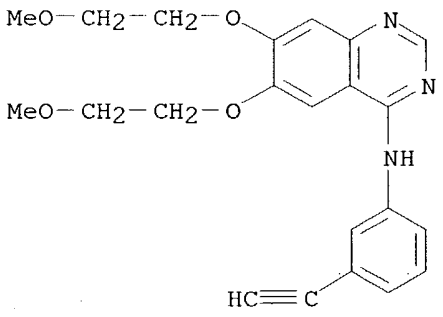
CRN (183321-74-6)



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93 REFERENCES IN FILE CA (1907 TO DATE)
95 REFERENCES IN FILE CAPLUS (1907 TO DATE)